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DEPRESSION OF GASTRIC SECRETION AND DIGESTION BY GASTRIC HYPOTHERMIA: ITS CLINICAL USE IN MASSIVE HEMATEMESIS

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THE depressive effect of cold on the activity of enzyme systems suggested that a study of the influence of hypothermia upon gastric secretion and digestion might provide helpful leads concerning mechanisms underlying the genesis of peptic ulcer and a useful guide in the control of masive hematemesis in man.[5]

Studies upon gastric digestion and secretion were made employing total body cooling as well as local (gastric) hypothermia. The sensitivity of esophageal epithelium to injury by gastric juice was described in 1948.[7] Perfusion of the normothermic cat's esophagus with gastric juice (20 cm. outflow pressure), obtained from patients having duodenal ulcer, results in perforation or evidence of severe esophagitis in approximately 75 per cent of instances.[4]

OBSERVATIONS

Cats.—The contrast between the observed effects of perfusion of gastric juice, obtained from patients with duodenal ulcer, in the esophagus of the normothermic and hypothermic cat is indicated in Table I. Perforation or evidence of severe esophagitis occurred in each of the 4 normothermic cats, whereas when the intraluminal temperature of the esophagus was kept at 20° C. by the use of systemic hypothermia little or no evidence of esophagitis was seen (Fig. 1). (See Addendum.)

Rats.—Table II indicates the striking difference in rapidity of digestion of 2 Gm. of raw beef in normothermic and hypothermic white rats after varying

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TABLE I. ESOPHAGEAL INJURY ATTENDING PERFUSION OF CAT'S NORMOTHERMIC AND HYPOTHERMIC ESOPHAGUS (2 HOURS) WITH GASTRIC JUICE FROM DUODENAL ULCER PATIENTS

GROUP	NUMBER OF CATS	RECTAL TEMPERATURE	TEMPERATURE WITHIN ESOPHAGUS	RESULTS*	
				NUMBER OF CATS	GRADE OF DIGESTION
Normothermic cats and gastric juice	4	37° C.	37° C.	3	5
				1	4
Hypothermic cats perfused with hypothermic juice (through ice bath)	6	25° C.	20° C.	4	1
				2	2

*Grading of esopheageal digestion: (1) areas of mucosal erosion; (2) areas of loss of mucosa with penetration into submucosa; (3) penetration into muscle layers; (4) penetration to outer layer of esophagus; and (5) free perforation through esophageal wall.

Fig. 1.—The sharp contrast between the effect of perfusion of the cat's esophagus with gastric juice obtained from patients with duodenal ulcer under normothermic and hypothermic conditions. In the normothermic cat, severe esophagitis or perforation occurred regularly; in the hypothermic cat, the damage to the esophageal mucosa was minimal. (See Table I.)

intervals of time. The rats were fasted for 24 hours and devoured the meat very promptly. By immersion of the group selected for cooling in ice water, rectal temperatures were observed to fall to a level of 20 to 25° C. in a few minutes.

TABLE II. WEIGHT LOSS OF 2 GM. MEAT MEAL IN NORMOTHERMIC AND HYPOTHERMIC WHITE RATS

GROUP	NUMBER OF ANIMALS	DURATION OF EXPERIMENT (HOURS)	GASTRIC RESIDUE IN GRAMS OF INITIAL 2 GM. MEAT MEAL	
			GRAMS (MEAN)	RANGE
Normothermic (rectal temperature 36.5° C.)	5	2-3	1.4	0.75-2.6
	4	4-5	0.5	0.0 -1.2
	13	6	0.04	0.0 -0.2
Hypothermic (rectal temperature 20 to 25° C.)	7	4-5	2.3*	1.8 -3.1
	10	6	2.3	1.6 -2.9
	5	12	1.8	0.7 -2.5

*Gain in weight owing to hydration of bolus.

Dogs.—Table III indicates the observed influence of temperature changes upon the progress of gastric digestion of meat in the dog. In the observations upon both dog and man reported herein, local gastric cooling was employed. The technique employed is described later in this paper.

TABLE III. GASTRIC DIGESTION OF MEAT BOLUS IN DOGS AT NORMAL AND HYPOTHERMIC (17° TO 20° C. SEROSAL TEMPERATURE) GASTRIC TEMPERATURES

NUMBER OF ANIMALS	DURATION (HOURS)	ANESTHESIA	PER CENT WEIGHT LOSS OF 2 GM. MEAT BOLUS AT:	
			37° C.	17° TO 20° C.
4	4	Pentothal	35	
4	6	Pentothal	55	
2	4	Flaxedil (gallamine triethiodide) and 1 per cent procaine		10
4	4	Flaxedil and 1 per cent procaine	25	
2	6	Flaxedil		25

Frogs.—The most striking influence of temperature upon the rate of digestion was observed in frogs, as is indicated in Table IV and Fig. 2. Small spring frogs *(Rana pipiens)* were placed headfirst into the stomachs of

TABLE IV. RATE OF GASTRIC DIGESTION OF LIVE RANA PIPIENS IN WARM (26° C.) AND COLD (2° C.) RANA CATESBEIANA

DURATION OF EXPERIMENT	DEGREE OF DIGESTION OF RANA PIPIENS	
	2° C.	26° C.
5 hours	Frog alive; skin intact	Skin and eyes gone; muscles exposed
6¾ hours	Frog alive; skin intact	Skin and eyes gone; peritoneal cavity open; muscle groups show beginning separation from skeleton
11 hours	Frog alive; skin intact	In addition to above, outline form gone; muscles disintegrating; 50 per cent mass gone
24 hours	Frog could not be revived; skin intact	Only skeleton remaining; 90 per cent mass gone
7 days	Skin eroded; peritoneum open, muscles intact	
72 hours (Decapitated frog)	No digestion even of exposed muscles	
10 hours (Pithed frog)		Marked digestion with body outline gone

Fig. 2.—Digestion of small spring frog (*Rana pipiens*) in large bullfrog (*Rana catesbeiana*) under normothermic and hypothermic conditions. *A*, At 6¾ hours, the small frog in cooled large frog is uninjured and very much alive; a frog of similar size implanted into the stomach of the normothermic large frog presents evidence of an advanced state of digestion. *B*, The situation at 24 hours. (See Table IV.)

normothermic and hypothermic large bullfrogs *(Rana catesbeiana)*. Whereas digestion of the smaller frog was well along and quite complete in the warm large frog after 5 hours, in the cold frog no evidence of digestion was discernible. In fact, small frogs subjected to intragastric placement in hypothermic large frogs survived apparently unharmed for as long as 11 hours—lending some credence to the Jonah story. At this interval, the recognizable outline of the frog placed in the warm larger frog was lost. After 24 hours in the stomach of the warm large frog, only portions of the skeleton of the introduced small frog could be identified. On the contrary, after 24 hours in the hypothermic larger frog, no evidence of digestion of the small frog was noted. This frog was still alive but did not survive. Even after a week's sojourn within the stomach of the hypothermic larger frog, the small frog exhibited only slight evidences of digestion.* The rate of digestion of decapitated or pithed frogs was essentially that of living frogs at the same temperature, giving no support to John Hunter's thesis of the importance of the "living principle" in affording tissues coming in contact with gastric juice protection against digestion.

Fish.—Table V provides information on the influence of temperature on gastric digestion in rainbow trout *(Salmo irideus)*. It is obvious that this fish possesses a surprisingly potent and rapid gastric digestive mechanism.

TABLE V. INFLUENCE OF TEMPERATURE ON GASTRIC DIGESTION IN RAINBOW TROUT (SALMO IRIDEUS)

DURATION OF EXPERIMENT (HOURS)	DEGREE OF DIGESTION OF TEST MINNOW AT:	
	2° C.	17.2° C.
1½	Skin intact; no digestion	Skin eroded; eyes shrunken; outline of minnow intact; muscles exposed
8	Skin eroded; eyes shrunken; outline intact; muscle exposed	Stomach contained only skin fragments
10	Outline recognizable; skin and head separated; fragment in intestine	
17	Small fragments remaining in stomach, many fragments in intestine	Only fragments of skin in distal intestine

A small minnow when placed in the stomach of a cold (2° C.) frog *(Rana catesbeiana)* showed no evidence of digestion after 9 hours, suggesting no increased susceptibility of the minnow to digestion.

TECHNIQUE OF LOCAL GASTRIC COOLING IN MAN AND DOG

Satisfactory lowering of the gastric temperature was obtained by perfusing a cold 50 per cent alcohol-water solution at low temperatures through a small thin-walled balloon attached to a double lumen tube which the patient swallowed. In addition, a nasogastric tube was placed into the stomach for gastric decompression. No studies were made employing systemic cooling in man because of the increased hazard of ventricular fibrillation at low body temperatures.

A refrigeration unit (Kelvinator DK-2S2SH) maintained the alcohol-water solution in a small open chamber at 2° to 5° C. This solution was pumped

*At 10° C., the small frog after twelve hours in the bullfrog's stomach showed skin losses only over bony prominences; after twenty-four hours, the skin of the test frog was digested, leaving muscles exposed.

into the intragastric-lying balloon through a No. 320 polyethylene tube with a lumen of 1 mm. The circulatory fluid returned to the chamber through the larger plastic outflow tube with an internal diameter of 6 mm. The rate of flow was regulated by a valve on the pump's intake side. The volume of fluid in the balloon and therefore the distension of the balloon were regulated by varying the backflow from the balloon. The maximum volume of solution that could be forced into the balloon was carefully predetermined by the volume in the cool chamber. The water level of fluid in this chamber was accurately regulated by a float arm connected to a microswitch which controlled the pump motor, responsible for the chamber-to-balloon circulation (Fig. 3).

The technique of securing total body cooling by use of local gastric hypothermia for intracranial operations was described by Barnard.[2] In our patients local cooling of the stomach only was obtained by surrounding the subject with warm blankets. The same technique was employed in the cooled dogs.

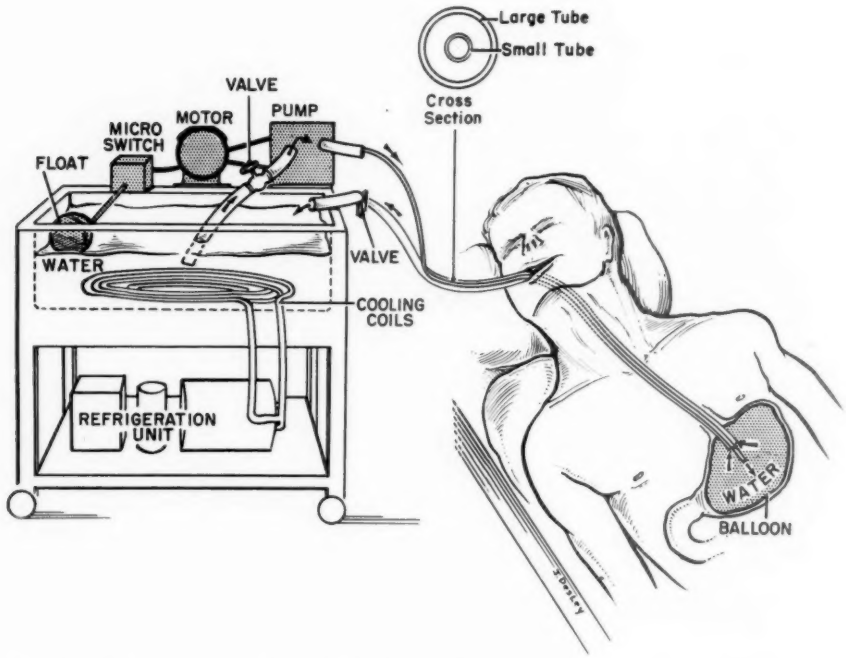

Fig. 3.—Schematic drawing of the device employed for obtaining local gastric hypothermia.

Determinations of the serosal gastric temperature in dogs showed there was ordinarily a temperature disparity of approximately 4° C.; the returning alcohol-water suspension was that much colder than the outside wall of the stomach. In the dog it was observed that the temperature 1 to 2 cm. away from the gastric wall was only 1° to 2° C. lower than that of the rectum. By this technique it was found relatively easy to maintain the body temperature at fairly normal levels. In the dog, a greater tendency for a downward drift of the rectal temperature was observed than in man.

OBSERVATIONS ON MAN

Table VI provides information on the influence of the gastric temperature in man upon the rapidity of digestion of a swallowed bolus of raw beef enclosed in a small porous tea bag with perforations. These observations suggest very definitely that local gastric hypothermia retards digestion in patients having the peptic ulcer diathesis.

TABLE VI. GASTRIC DIGESTION IN MAN AT NORMAL AND HYPOTHERMIC (OUTFLOW TEMPERATURE 13° TO 16° C.)* GASTRIC TEMPERATURE

PATIENT	DIAGNOSIS	DURATION OF EXPERIMENT (HOURS)	MEAN PER CENT WEIGHT LOSS OF 2 GM. MEAT BOLUS AT:	
			NORMOTHERMIC TEMPERATURE	HYPOTHERMIC TEMPERATURE (17° TO 20° C.)
Mrs. M. P.	Varicose veins	4	25	20
Mrs. M. F.	Duodenal ulcer	4	90	30
Mrs. J. M.	Duodenal ulcer	4	45	25
Mr. J. N.	Gastric ulcer	8	66	5
Mr. P. D.	Postgastrectomy	4	70	50

*Gastric serosal temperatures in dogs approximately 4° C. higher than outflow temperature.

In Table VII, the influence of temperature upon the in vitro digestion of 10 Gm. of raw beef when submerged in warm and cold gastric juice is to be noted. The agreement between the observed differences obtaining in vivo and in vitro rapidity of gastric digestion, as influenced by temperature under conditions of the experiments (Tables VI and VII), is striking.

TABLE VII. DIGESTION OF 10 GM. MEAT BOLUS AT BODY (38° C.) AND LOW TEMPERATURE (8° C.) IN GASTRIC JUICE OBTAINED FROM 2 PATIENTS WITH DUODENAL ULCER

PATIENT	DIAGNOSIS	DURATION OF IMMERSION OF BOLUS IN GASTRIC JUICE (HOURS)	PER CENT OF WEIGHT OF MEAT BOLUS AT:		REMARKS
			38°C.	8°C.	
Mrs. M. F.	Duodenal ulcer	6	−21	+11	Meat unchanged at low temperature but increased weight probably due to hydration
Mr. A. R.	Duodenal ulcer	4	−50	+25	

Table VIII provides information on observed differences in volume of gastric secretion as influenced by gastric temperature in the dog. It is to be

TABLE VIII. GASTRIC SECRETION IN DOGS AT NORMAL AND HYPOTHERMIC (17° TO 20° C.) GASTRIC TEMPERATURE

DURATION OF COOLING (HOURS)	NUMBER OF DOGS	MEAN PER CENT VOLUME DECREASE (RANGE 50-95)	pH	PER CENT DECREASE FREE HCl (RANGE 31-96)	PER CENT DECREASE PEPSIN (RANGE 21-95)
4 to 5	5	75	No change*	75	63
3	1	85	No change	86	85
5	1 (Heidenhain pouch)	64	No change	47	82

*The observed pH before and after cooling remained unchanged and varied between 1.2 and 1.8.

TABLE IX. GASTRIC SECRETION IN MAN AT NORMAL AND HYPOTHERMIC GASTRIC TEMPERATURES (OUTFLOW TEMPERATURE 13° TO 16° C.)

PATIENT	DIAGNOSIS	PER CENT VOLUME DECREASE	PER CENT DECREASE IN FREE HCl	PER CENT PEPSIN DECREASE
Mr. J. J.	Duodenal ulcer	40	100	46
Mr. P. D.	Prior gastric resection for duodenal ulcer	94	No free HCl present	83

TABLE X. PRESENT LIMITED EXPERIENCE IN MAN OF MANAGEMENT OF MASSIVE HEMATEMESIS BY LOCAL GASTRIC HYPOTHERMIA

PATIENT	AGE	DIAGNOSIS	INITIAL CONDITION	LENGTH OF COOLING (HOURS)	OUTFLOW TEMPERATURE RANGE	RESULT
Mrs. M. L.	76	Severe massive hematemesis from unconfirmed duodenal ulcer	Hemoglobin 9.7 Gm. after transfusion of 2,500 c.c. of blood	6½	15° to 20° C. Mean 18.5	Cessation of hemorrhage; hemoglobin sustained; additional transfusion of 2,500 c.c. brought hemoglobin to 16.3 Gm. on discharge and no subsequent bleeding
Mr. J. J.	32	Massive hematemesis from duodenal ulcer	Shock; blood pressure 86/50; pulse 100; dehydrated; hemoglobin 11 Gm.	8½	11.5° to 16.5° C. Mean 15	Cessation of hemorrhage; 3,000 c.c. blood transfused; discharged with hemoglobin of 14.3 Gm.
Mr. E. Z.	41	Recurrent ulcer following gastrectomy	Shock; hemoglobin 5.5 Gm.; blood presure 92/68; pulse 100	5½	13° to 18° C. Mean 15	Cessation of hemorrhage; 2,000 c.c. blood transfused; hemoglobin stabilized at 14 Gm.; discharged for observation; no further bleeding
Mr. L. R.	56	Alcoholic cirrhosis	Third hospitalization; short period of shock following initial hemorrhage; hemoglobin 10.5 Gm. 3,000 c.c. of blood transfused; severe icterus; large ascites; signs of liver failure and impending coma	125		Prompt cessation of hemorrhage; hemoglobin sustained at 12 Gm. with daily transfusions of 250 c.c. blood; no effect on hepatic coma
Mrs. E. C.	81	Metastatic carcinoma inguinal nodes, primary site unknown; essential hypertension (180/110). Probable duodenal ulcer	Massive hematemesis; shock; blood pressure 100/60; pulse 100; hemoglobin 8.7 after 1,000 c.c. blood transfusion	20	12° to 20° C. Mean 17	Prompt cessation of hemorrhage; hemoglobin to 14 Gm. after 2,000 cc. blood transfusion; no further bleeding

noted that, whereas hypothermia failed to influence the pH, it did reduce very significantly the amount of acid secreted essentially because of the lesser volume.

Table IX indicates that local gastric cooling in man depresses the volume of secretion considerably. The reduction in amount of free HCl secreted is owing largely, probably, to reduction in volume of secretion as in the dog.

The observed depression of gastric digestion is owing undoubtedly to the inhibition of pepsin action at the low temperatures employed. Using the radioactive iodinated serum albumin method,[1] the proteolytic activity of an 0.05 mg. per cubic centimeter pepsin solution was determined over the temperature range of 2° to 37° C. Pepsin at 17° C. was found to be approximately one-fourth as active as at 37° C. At 2° C. pepsin is only one-tenth as active as at 37° C.

GASTRIC COOLING FOR MASSIVE HEMATEMESIS

Table X summarizes our experience with the treatment of massive gastric hemorrhage in 5 patients. These observations suggest that local gastric hypothermia favorably influences the arrest of hemorrhage of acid-peptic origin. One additional patient beyond the four shown in Table X was subjected to local gastric hypothermia. This woman, aged 49, had a large gastric cancer and presented thrombocytopenia and purpura as well as hematemesis; the blood dyscrasia was owing to widespread osseous metastases and hypersplenism. Prepared sections of the bone marrow aspirate revealed metastatic tumor cells. Attending gastric cooling, there was temporary cessation of the gastric hemorrhage and improvement of the patient's condition. She and the family refused an abdominal exploration for splenectomy and palliative gastric resection. Gastric hemorrhage recurred but no serious effort could be made to staunch the bleeding in the light of the family's attitude toward the situation. The suggestion made many years ago[3, 6] that bleeding from esophageal varices in the presence of portal hypertension is essentially acid-peptic in nature appears to receive some support in cessation of hemorrhage in the limited experience recorded in Table X.

CONCLUSIONS

The observations recorded herein suggest that gastric temperatures of the order of 17° to 20° C. depress gastric secretion and impede the gastric digestive process materially. Local gastric hypothermia can be achieved by relatively simple means and can be employed apparently without hazard. No gross or microscopic evidence of injury to the gastric mucosa has been observed after prolonged gastric cooling in the dog. It is believed that local gastric cooling can be a useful therapeutic agency in the control of massive hematemesis of acid-peptic origin. It should prove to be a measure of real value in readying patients with active massive gastric hemorrhage for operation by inhibiting peptic activity and arresting hemorrhage, permitting stabilization of vital signs with restoration of a fairly normal blood volume. Thus the surgeon is afforded an opportunity to deal with a potentially serious situation under more favorable circumstances. Only an increased experience with the method will define more precisely its advantages and limitations.

We wish to acknowledge helpful advice from Dr. C. N. Barnard, erstwhile Surgical Fellow of this Clinic, in the assembly of the cooling unit and to Mr. Clarence Gunther, Surgical Research Laboratory Supervisor, for his ingenuity in adapting materials and techniques to the needs of this study.

ADDENDUM

Perfusion of the cat's esophagus with 0.1 N, 2 N, 4 N, and 6 N HCl without pepsin in both normothermic (37° C. rectal and intraesophageal temperature) and hypothermic (25° C. rectal and 20° C. intraesophageal temperature) animals produced essentially identical degrees of esophageal damage at comparable acid concentrations.

The esophageal changes ranged from no effect at 0.1 N HCl through increasingly severe burning at 2 N and 4 N HCl to rapid perforation and fragmentation of the esophagus at 6 N HCl. Hypothermia provided no protection to the cat's esophagus against damage by HCl.

Observations are also under way to assess whether or not cooling affords any promise of protection in the enzymatic process of acute experimental pancreatic necrosis.

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EXPERIENCES WITH THE RETROSTERNAL ESOPHAGEAL REPLACEMENT EMPLOYING JEJUNUM OR ILEUM

An Analysis of 28 Cases

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HITHERTO, numerous methods of jejunal mobilization for the reconstruction of the esophagus have been described, such as those of Roux,[25] Hertzen,[10] Yudin,[31, 32] Petrov and Khundadze,[20, 21] Dubost and Bernier,[7] Ballivet,[2] Van Prohaska and Sloan,[30] Shalimov,[28] Shumacker and Battersby,[29] Harrison,[9] Rienhoff,[23] Kramarenko,[15] Longmire,[17] and Androsov.[1]

There are many advantages to utilizing the small intestine for construction of a total new esophagus. However, in such operations the problem of mobilization of a sufficiently long and well-vascularized jejunal loop is a real one. Our first opportunity to utilize the jejunum for this purpose was in 1949; however, in earlier cases of anterior thoracic subcutaneous esophagoplasty we were able to bring the jejunum only to the height of the third or first rib. Since 1951 we have been able to mobilize the jejunum in almost all cases to the cervical regions and sometimes beyond. We attribute these achievements to knowledge gained from experience with the procedure and to the recognition of many pertinent anatomic details from study of human cadavers. In addition, angiographic studies of the intestinal arterial and venous vasculature as well as to the use of our method of jejunal mobilization in the cervical direction have been important.

The main principles of mobilization of a convenient jejunal loop in an isoperistaltic manner with preservation of its blood supply are as follows: (1) selection of a proper jejunal artery and vein supplying the intestinal segment to be used for the esophagoplasty, after inspection of the first 6 primary jejunal vessels and their arcades; (2) separate section of the jejunal arteries and veins because of their different courses; (3) division of the jejunal arteries and veins close to the root of the superior mesenteric vessels (this allows for greater elongation of the mobilized jejunum without damage to the lower vascular arcades); (4) after compression to test for adequacy of the circulation, division of only that number of vessels which will allow for mobilization and yet insure an adequate blood supply (this should not exceed 2 or 3 vessels); (5) adequate division of the intervening peritoneum in the intravascular spaces; and (6) in those cases in which the mobilized jejunum is not sufficiently long after division of the jejunal vessels in the above described manner, additional length gained by displacing the trunk of the superior mesenteric vessels in a cephalad direction with or without division of the ileocolic vessel. This method summarizes the advantages of the technique described by Petrov and Khundadze,[20] and Dubost and Bernier,[7] on the one hand, and that of Ballivet,[2] on

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the other. This allows the cephalad displacement of the superior mesenteric vessels and simultaneously permits the course of the jejunal vessels to be changed from an obliquely downward to an obliquely upward course. Moreover, it secures the fixation of this displacement.[13, 14] Because mobilization of the bowel in the above described manner yielded such satisfactory results, we were induced to perform esophagoplasty in a transthoracic rather than an anterior thoracic fashion.

Among the many available methods for transthoracic mobilization of the intestine through the left or right hemithorax or the posterior or anterior mediastinum, we have chosen the one described independently by Eremeev[8] and Robertson and Sarjeant.[24]

From dissections on human cadavers, undertaken to establish approximately the extent of particular procedures, eventual technical difficulties, and the most suitable length of passage, it was found that the retrosternal approach was the most suitable for these purposes. A substitute retrosternal esophagus made from jejunum was subsequently created during the years 1953 to 1956 on 23 patients with cicatricial stricture or obliteration of the esophagus following caustic burns. In addition, a retrosternal substitute esophagus has been constructed in 5 patients utilizing the ileum with a small part of the cecum conserving the ileocecal valve. In contrast to the technique utilized by French authors,[6, 12, 16, 26] this latter procedure consisted in using a sufficiently long loop of the ileum with the ileocecal valve and suspending the mobilized portion of the ileum on the ileocolic vessels. A small caput of the cecum is anastomosed to the stomach, the ileocecal valve functioning as an artificial cardia. Angiographic studies on human cadavers demonstrated that contrast medium injected through the ileocolic vessels fills the whole trunk of the superior mesenteric vessels even under low pressure. It is believed that this method compares favorably with other recommended methods for esophageal reconstruction utilizing the bowel. A more detailed description of the procedure and its advantages will be given in a separate report (Fig. 1).

CLINICAL MATERIAL

Twenty-eight patients operated upon have come from all parts of Poland to our Clinic at various times after chemical burn of the esophagus. All had been previously treated on laryngologic or surgical services elsewhere by dilatations with indifferent results. Most of the patients had been nourished by gastrostomy for many months to years. Therefore, in all patients there were absolute indications for surgical treatment.

The construction of an artificial esophagus was divided as a rule into 2 stages. At the first stage mobilization of the jejunum or ileum was carried out and an intra-abdominal anastomosis between stomach and bowel was made after pulling the small bowel through the mesocolon. Next the retrosternal tunnel was dissected and the mobilized intestine was passed cephalad through it to the cervical region. At the second operation, the esophagojejunal or esophagoileal anastomosis in the cervical region was made. Delayed anastomosis between the esophagus and transplanted intestine in the cervical region

at a second operation 2 to 4 weeks later is undoubtedly a safer procedure than when carried out at a primary operation. Four patients required a third operation for anastomosis between transplanted jejunum and stomach and

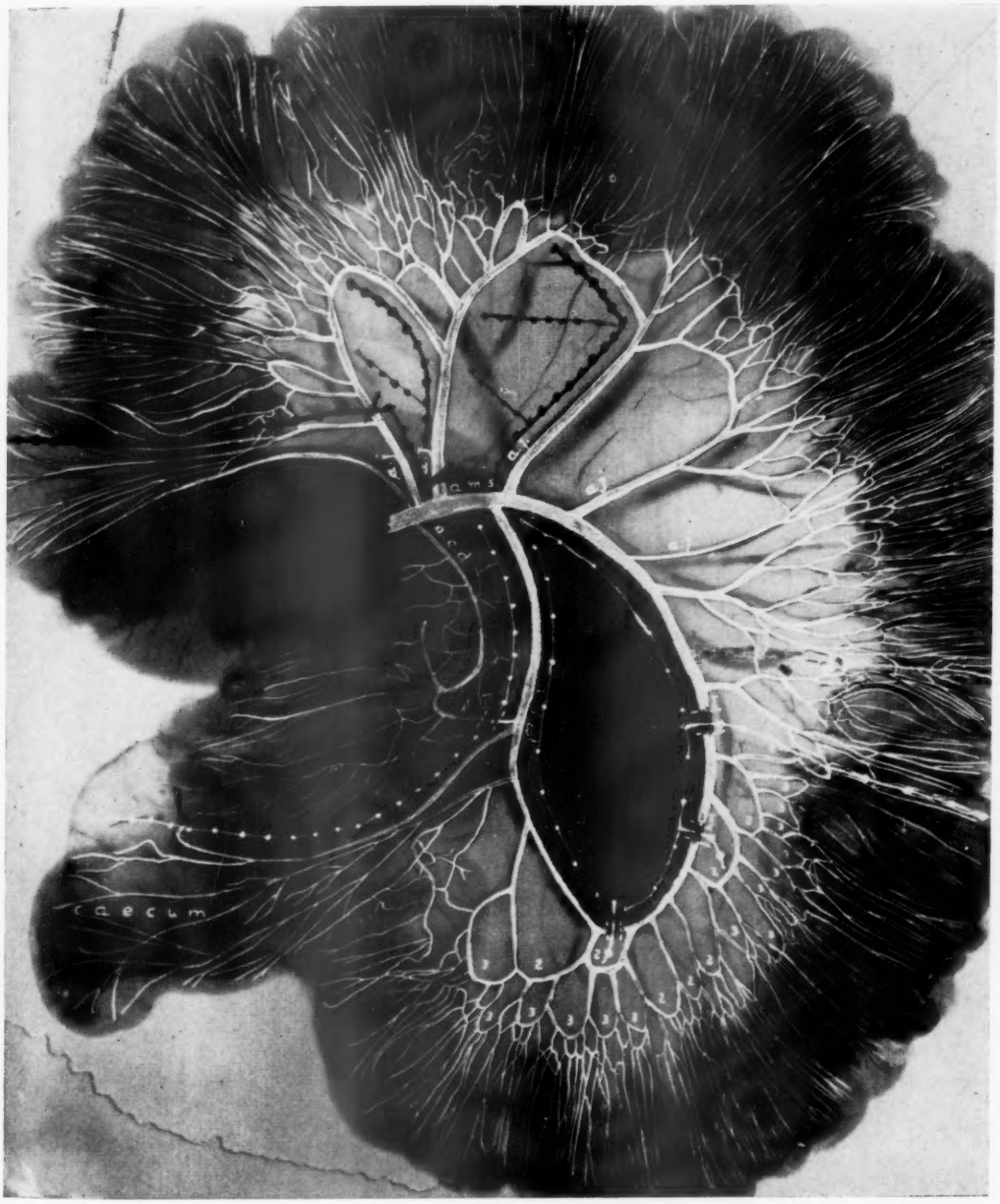

Fig. 1.—Diagram made from an angiogram of the superior mesenteric artery illustrating the methods of mobilization of the jejunum or ileum and cecum for esophageal replacement. Black dotted lines indicate dissections for jejunal mobilization; white dotted lines indicate dissections for ileocecal mobilization. a.m.s., superior mesenteric artery; a.j., jejunal artery; a.il-col., ileocolic artery; a.c.d., right colic artery.

another for a partial gastric resection for pyloric stenosis. The course of the operative treatment and the results of the entire group of 28 patients are summarized in Tables I and II.

TABLE I. RETROSTERNAL ESOPHAGEAL REPLA

FIRST STAGE

SERIAL NUMBER	PATIENT	AGE AND SEX	PREVIOUS PROCEDURES	DATE	DIVISION OF JEJUNAL VESSELS (NUMBER)			ABDOMINAL ANASTOMOSES		
					ONLY	DISPLACED TRUNK OF THE SUPERIOR MESENTERIC VESSELS	ADDITIONAL DIVISION OF ILEOCOLIC VESSELS	ENTERO-ENTERO ONLY	ENTERO-ENTERO AND JEJUNOGASTRO	ENTERO-ENTERO AND JEJUNOGASTRO WITH EXCISION OF A JEJUNAL SEGMENT
1	D. E.	11 M	Dilatations, gastrostomy	June 9, 1953		+ /2/			+	
2	W. L.	51 F	Extirpation of the thoracic esophagus (Ca susp.), gastrostomy	Sept. 17, 1953		+ /2/			+	
3	M. C.	47 M	Dilatations, gastrostomy	March 6, 1954			+ /2/		+	
4	S. C.	50 M	Dilatations, gastrostomy	April 1, 1954		+ /2/			+	
5	M. F.	25 M	Exploratory thoracotomy, gastrostomy	April 1, 1954		+ /2/			+	
6	Z. D.	7 F	Dilatations, gastrostomy	Oct. 30, 1954		+ /2/			+	
7	L. A.	27 F	Dilatations, gastrostomy	Oct. 11, 1954		+ /2/			+	
8	P. A.	6 M	Dilatations, gastrostomy	Oct. 19, 1954		+ /2/			+	
9	R. K.	10 M	Dilatations, gastrostomy	Jan. 20, 1955		+ /2/			+	
10	W. D.	27 F	Dilatations, gastrostomy	May 5, 1955			+ /3/	+		
11	Z. W.	10 M	Dilatations, gastrostomy	May 7, 1955		+ /2/			+	
12	L. J.	4 M	Dilatations, gastrostomy	May 12, 1955	+ /3/				+	
13	K. E.	5 F	Dilatations, gastrostomy	July 16, 1955	+ /1/					+
14	M. R.	4 F	Dilatations, gastrostomy	Oct. 10, 1955		+ /1/				+

REPLACEMENT EMPLOYING JEJUNUM

STAGE		SECOND STAGE						
			CERVICAL ESOPHAGO-JEJUNOSTOMY					
RETROSTERNAL DISSECTION	COMPLICATIONS	DATE	END-TO-END	END-TO-SIDE	SIDE-TO-SIDE	COMPLICATIONS	OTHER OPERATIONS	RESULTS
With pneumothorax on one side	0	June 20, 1953		+		Temporary anastomotic leak	0	Very good
Without pneumothorax	0	Oct. 9, 1953	+			0	0	Very good
Without pneumothorax	0	April 6, 1954		+		0	0	Very good
Without pneumothorax	0	April 22, 1954		+		0	0	Early good Death 4 mo. after discharge date (pneumonia)
Without pneumothorax	0	June 24, 1954			+	0	0	Very good
Without pneumothorax	Loss of a cervical part of transplanted jejunum	Feb. 25, 1956, remobilization of the jejunum from anterior mediastinum	+			0	0	Very good
Temporary transplantation under skin; Nov. 11, 1954, remobilization of the jejunum and trasplantation through the anterior mediastinum	0	Dec. 9, 1954		+		Temporary anastomotic leak	0	Very good
Without pneumothorax	0	Nov. 9, 1954			+	0	0	Very good
Without pneumothorax	0	Feb. 10, 1955		+		0	0	Very good
Without pneumothorax	0	May 30, 1955	+			0	July 2, 1955, jejunogastroanastomosis	Very good
Without pneumothorax	0	May 31, 1955		+		0	0	Very good
With pneumothorax on one side	0	June 14, 1955			+	0	0	Very good
With pneumothorax on both sides	0	Oct. 4, 1955		+		0	0	Very good
Without pneumothorax	0	Nov. 3, 1955		+		0	0	Very good

TABLE I—C

FIRST STAG

SERIAL NUMBER	PATIENT	AGE AND SEX	PREVIOUS PROCEDURES	DATE	DIVISION OF JEJUNAL VESSELS (NUMBER)			ABDOMINAL ANASTOMOSES		
					ONLY	DISPLACED TRUNK OF THE SUPERIOR MESENTERIC VESSELS	ADDITIONAL DIVISION OF ILEOCOLIC VESSELS	ENTERO-ENTERO ONLY	ENTERO-ENTERO AND JEJUNO-GASTRO	ENTERO-ENTERO AND JEJUNOGASTRO WITH EXCISION OF A JEJUNAL SEGMENT
15	K. E.	4 M	Dilatations, gastrostomy	May 28, 1955	+ /2/				+	
16	T. M.	7 F	Dilatations, gastrostomy	Nov. 10, 1955			+ /2/			+
17	P. J.	4 F	Dilatations, gastrostomy	Nov. 22, 1955	+ /1/					+
18	O. S.	2½ M	Dilatations, gastrostomy	Jan. 17, 1956			+ /2/			+
19	P. A.	33 F	Dilatations, duodenostomy (pyloric stenosis)	Jan. 21, 1956	+ /2/			+		
20	G. T.	4 M	Dilatations, gastrostomy	Feb. 18, 1956		+ /2/		+		
21	P. J.	14 M	Dilatations, gastrostomy	April 17, 1956			+ /2/	+		
22	P. G.	31 F	Dilatations, gastrostomy	June 13, 1956	+ /2/				+	
23	K. H.	4 M	Dilatations, gastrostomy	Oct. 16, 1956	+ /1/			+		

At this time there are few reports of sizable series of cases operated upon by the above-mentioned methods. Those of Eremeev,[8] Robertson and Sarjeant,[24] Savinykh,[27] Michaud and Margotten,[18] Petrov,[19, 22] Holinger,[11] Betts,[3, 4] Carswell, Hays and Viar,[5] and ours[13, 14] may be cited, however. Several points of technical importance in construction of a substitute retrosternal esophagus have been emphasized by the above-mentioned authors. In this communication attention will be directed primarily to problems concerning retrosternal esophageal replacement utilizing small intestine.

I—Cont'd

STAGE		SECOND STAGE						
			CERVICAL ESOPHAGO-JEJUNOSTOMY					
RETROSTERNAL DISSECTION	COMPLICATIONS	DATE	END-TO-END	END-TO-SIDE	SIDE-TO-SIDE	COMPLICATIONS	OTHER OPERATIONS	RESULTS
Without pneumothorax	0	June 25, 1955		+		0	0	Very good
Without pneumothorax	0	Dec. 1, 1955	+			Stenosis of the anastomosis	Dec. 31, 1955, excision of the cervical anastomosis, reanastomosis	Very good
Without pneumothorax	0	Dec. 13, 1955	+			0	Obstruction of the artificial esophagus after 4 mo., mediastinotomy	Early good Late very good
Without pneumothorax	Death in the first postoperative day, pneumonia dispersa							
Without pneumothorax	0	Feb. 7, 1956	+			0	March 9, 1956, partial gastric resection and anastomosis between the stomach and transplanted jejunum end-to-side	Very good
Without pneumothorax	0	March 6, 1956	+			0	April 19, 1956, excision of an abdominal jejunal segment and jejunogastroanastomosis	Very good
With pneumothorax on one side	0	May 8, 1956	+			Temporary anastomotic leak	June 9, 1956, jejunogastroanastomosis	Very good
With pneumothorax on one side	0	July 3, 1956	+			Temporary anastomotic leak	0	Very good
Without pneumothorax	0	Nov. 17, 1956	+			Temporary anastomotic leak	Dec. 20, 1956, jejunogastroanastomosis	Very good

The retrosternal tunnel is constructed only after careful and successful mobilization of the intestine and restoration of the continuity of the digestive tract. After mobilization of the jejunum it is placed in the retrosternal tunnel prior to gastrojejunal anastomosis as it is difficult to determine the level at which the anastomosis should be made by extrathoracic measurement. In some cases wherein the jejunum had been placed into the anterior mediastinum following the restoration of intestinal continuity and gastrojejunostomy, there was an excess of jejunal loops above the gastroenterostomy. In one of these

TABLE II. RETROSTERNAL ESOPHAGEAL REPLACEMENT EMPLOYING ILEUM WITH A SMALL PART OF CECUM

SERIAL NUMBER	PATIENT	AGE AND SEX	PREVIOUS PROCEDURES	FIRST STAGE			SECOND STAGE			RESULTS
				DATE	RETROSTERNAL DISSECTION	COMPLICATIONS	DATE	CERVICAL ESOPHAGO-ILEOSTOMY	COMPLICATIONS	
1	P. G.	11 M	Antethoracic esophagoplasty; necrosis of one-half of transplanted jejunum	Oct. 27, 1956	Without pneumothorax	0	Nov. 19, 1956	End-to-end	0	Very good
2	C. H.	6 F	Dilatations, gastrostomy	Oct. 8, 1956	With pneumothorax on left side	Gastric hemorrhage	Dec. 13, 1956	End-to-end	0 April 9, 1957, ileus, operative treatment	Very good
3	M. S.	6 M	Dilatations, gastrostomy	Feb. 19, 1957	Without pneumothorax	0	March 23, 1957	End-to-side	Temporary anastomotic leak	Very good
4	P. M.	4 F	Dilatations, gastrostomy	March 2, 1957	Without pneumothorax	0	April 2, 1957	End-to-end	0	Very good
5	N. B.	10 F	Dilatations, gastrostomy	March 30, 1957	Without pneumothorax	0	April 24, 1957	End-to-end	0	Very good

cases (Table I, Case 17) this resulted in kinking of the transplanted jejunum in the lower part of the retrosternal tunnel. After a period of 4 months this led to obstruction of the esophageal replacement. Therefore, after transplantation of the jejunum through the retrosternal tunnel, as much redundant intestine as possible should be drawn back gently into the abdomen and placed below the level of the proposed gastrojejunal anastomosis. The length of the intestine is always greater than that of the mesentery. In several cases we have attempted to excise an abdominal part and, in the last year, a thoracic part of the mobilized jejunum or ileum in order to straighten out the bowel and thereby avoid the tortuous course of intestine which otherwise may result.

The retrosternal tunnel is constructed by beginning the dissection in the abdomen and also in the cervical area. After incising the skin and exposing the xiphoid process the peritoneum is separated from the diaphragm and the edges of the rectus muscles in the region of the costal arches. The diaphragm is separated from its attachments to the sternum and costal margin to the width of 7 cm. The dissection is carried along the posterior wall of the sternum, with the parietal pericardium being pushed down on either side. Unlike other authors, we have never removed the xiphoid process since we do not feel this is necessary. The cervical incision is made along the anterior border of the sternocleidomastoid muscle. The deep cervical fascia is incised and the sternohyoid and sternothyroid muscles are divided close to the sternum. Next, the mediastinal fatty tissue is separated in the midline close to the under surface of the sternum. The retrosternal passageway is then widened laterally to dimensions sufficient to allow passage for the mobilized intestine with its mesentery. In positioning the intestine in the retrosternal tunnel, the bowel is placed to the left and the mesentery to the right side. In the cervical region the intestine is made to lie transversely from left to right in a subcutaneous pocket. This position of the intestine reduces the tension on the vascular arcades.

In several cases the aperture of the retrosternal tunnel below the cervical region has been too narrow in an anterior-posterior dimension. This occurred especially in patients whose manubrium sloped obliquely toward the body of the sternum. Swelling and cyanosis of the end of the transplanted bowel resulted. In such patients a slot has been cut in the manubrium. The mesentery of the mobilized intestine is allowed to lie in this slot, thereby reducing pressure on vessels, especially the veins.

Pneumothorax on one or both sides may occur during the retrosternal dissection. Damage to the pleura occurs for the most part during the mid-portion of the retrosternal dissection, since the procedure must be done without adequate visualization. This complication constitutes no particular hazard for the patient if intratracheal anesthesia is utilized. Pleural holes are rapidly closed by adherence of the intestine in the retrosternal tunnel. After operation radiographic examination of the thorax should be performed, seeking especially pneumothroax, as this complication is likely to be overlooked during the operation since it may occur even in the absence of evident damage to the pleura.

To avoid grave complications in the postoperative period, only segments of intestine with good blood supply throughout the length are pulled through the retrosternal tunnel. For instances of doubtful blood supply the intestine may be placed in a subcutaneous tunnel (as in Case 1, Table II). This technique is likewise applicable for those patients whose intestine (jejunum) after mobilization does not reach the neck easily (as in Case 7, Table I). Some weeks later the jejunum can be secondarily separated from the subcutaneous tissue and transferred to the transthoracic substernal position (Case 7, Table I). Such a procedure we have termed "biphasic ante- and retrosternal jejunal transplantation." This will prevent the complications due to necrosis which might attend primary transthoracic procedures.

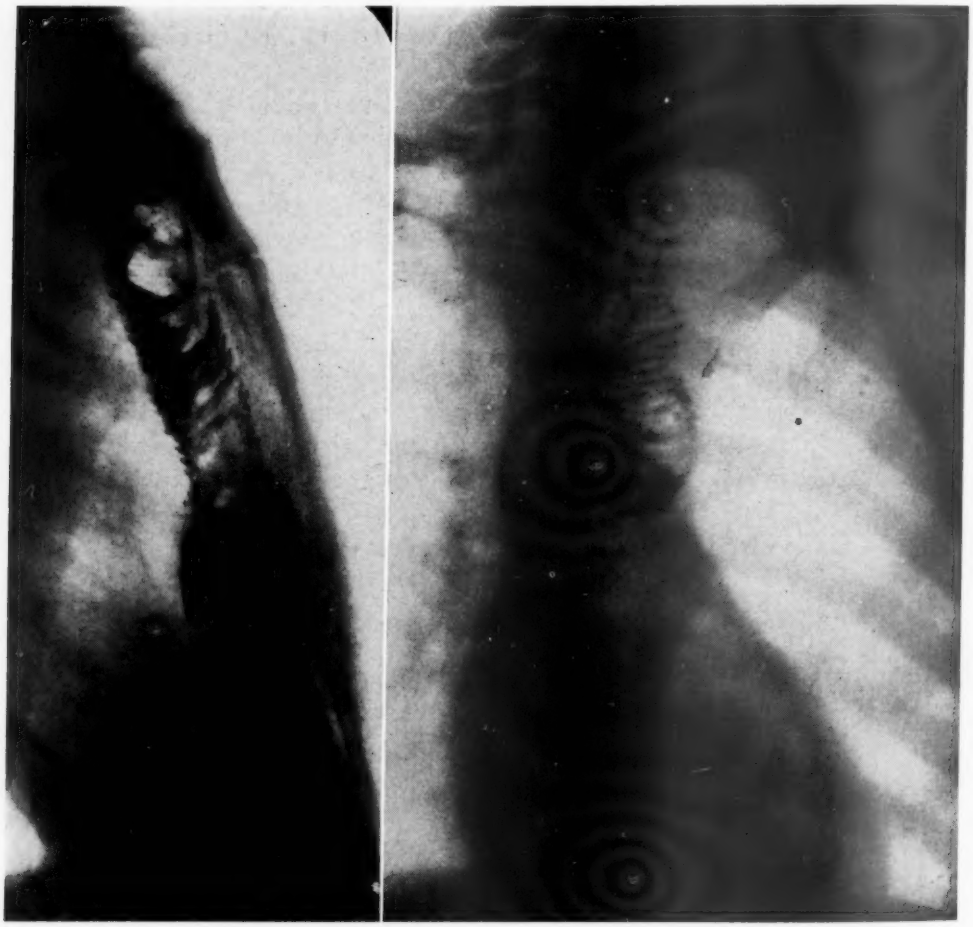

Fig. 2. Fig. 3.

Fig. 2.—Lateral roentgenogram taken after barium swallow (Case No. 3, Table I).
Fig. 3.—Anteroposterior roentgenogram after barium swallow showing mobilized intestinal segment (Case No. 16, Table I).

Necrosis of the entire transplanted intestine is a very serious complication. We have never observed such a complication. However, should this occur, early diagnosis is imperative and immediate removal of the necrotic segment is to be undertaken. Necrosis of the cephalad end of the transplanted jejunum in the

anterior mediastinum constitutes a minor hazard. This may occur and the patient may manifest an asymptomatic course if antibiotics are used (Case 6, Table I). However such a complication makes restoration of alimentary continuity very difficult. In such cases the viable end of the jejunum may be mobilized through one of the intercostal spaces with completion of the operation by a cutaneous tube, or, better, the jejunum may be repeatedly mobilized in the anterior mediastinum and again be transferred through it into the cervical region. This can be accomplished by the additional section of one or two jejunal vessels (Holinger and associates[11]) or even without this (Case 6, Table I).

CONCLUSIONS

On the basis of examinations of human cadavers, clinical observations, and a review of the literature, we feel that the creation of a total retrosternal esophagus from the small bowel has several advantages over other methods. Compared with other transthoracic methods, this procedure is simple to perform technically, is not so extensive, and is well tolerated. It does not require opening the pleural cavity. Mobilization of the intestine into the anterior mediastinum creates no side effects from the thoracic viscera. Moreover, the intestinal limb in the anterior mediastinum can be comparatively short. It is easily accessible from the cervical region, abdomen, or through longitudinal division of the lower part of the sternum (median sternotomy). This is of importance in cases of early and remote complications as, for example, necrosis of a part of the jejunum after its transplantation, occlusion of its lumen, or in the presence of swallowed foreign bodies.

As compared with antethoracic procedures the results of retrosternal esophagoplasty as described are far better both from a functional and cosmetic standpoint. This latter consideration is of importance especially for young individuals. (Figs. 2 and 3.)

SUMMARY

Experience in construction of a retrosternal esophagus from jejunum in 23 patients and from ileum and cecum in 5 patients is reported. The hospital course, operative procedure, and results are summarized.

The creation of a retrosternal esophagus from small bowel is simple technically compared with other transthoracic procedures, is not so extensive, and is well tolerated by the patient. When compared with the antethoracic method, the functional and cosmetic results of retrosternal esophagoplasty are far better.

We wish to thank Dr. J. F. Perry, Jr., of the Surgical Clinic at the University of Minnesota for help in effecting editorial revision of the paper.

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ADDENDUM

At present we have completed 32 total retrosternal esophageal replacements from the small intestine.

AN EXPERIMENTAL STUDY OF IRON ABSORPTION FOLLOWING TOTAL GASTRECTOMY

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HYPOCHROMIC anemia has been observed in both humans and dogs following total gastrectomy. Such an anemia usually responds favorably to iron therapy. Long-continued loss of small amounts of blood from esophagitis, impaired absorption of iron in the small intestine, or a combination of these factors have all been suggested as causes for this sort of anemia. Mettier and associates[4] and Mullenix and co-workers[5] have proved that the ability of the dog to produce hemoglobin decreases after total gastrectomy and that the oral administration of iron results in a marked increase in the production of hemoglobin.

Anemia resulting from iron deficiency also has occurred following subtotal gastrectomy.[1, 3, 6] Jasinski and Ott[1] have pointed out the similarity between gastrointestinal symptoms produced by iron deficiency and some of the symptoms that occur after gastrectomy.

This series of experiments was carried out to determine the adequacy of the absorption of iron following total gastrectomy.

Experiment No. 1. Comparison of Oral Iron Tolerance Tests Before and After Production of Anemia by Bleeding.—

Method: Iron absorption tests were done on 7 adult mongrel dogs, 1 to 4 years after total gastrectomy. Six normal adult dogs and one subtotally gastrectomized dog were used as control animals. All dogs were maintained on the usual kennel ration during this study. Each experiment was started in the early morning after a 16-hour fast. During the 8-hour iron absorption study the animals were not allowed to eat. Two milligrams of elemental iron per kilogram of body weight was administered by mouth to all animals in the form of ferrous ammonium sulfate. Blood specimens were taken prior to giving the iron and 30, 60, 150, 240, 360, and 480 minutes after the iron was given. Plasma iron was determined by the method of Kitzes.[2] Following these initial studies 100 to 300 ml. of blood was removed from the animals at various intervals over a period of 17 to 35 days, in order to maintain a level of hemoglobin between 4.5 and 7.5 Gm. per cent. The iron absorption studies were then repeated.

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Results: In Fig. 1 the absorption of iron in nonanemic, normal dogs is compared to that of nonanemic, totally gastrectomized dogs. The mean fasting plasma levels of iron in the 2 groups are identical, but at one-half and one hour following administration of iron they are somewhat higher for the gastrectomized animals. At later periods there is no significant difference in levels of plasma iron between the 2 groups.

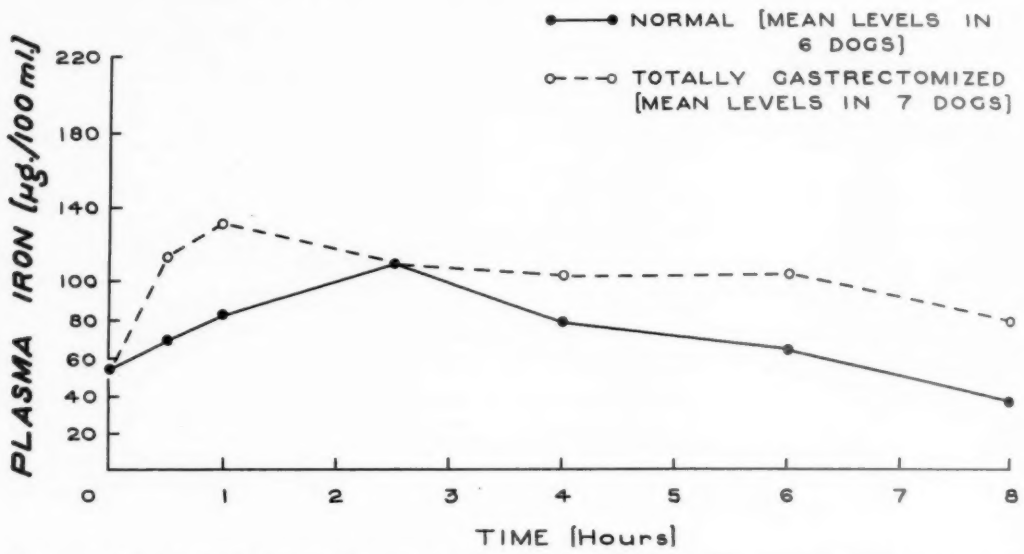

Fig. 1.—Plasma iron levels in normal and totally gastrectomized dogs following oral administration of 2 mg. of iron per kilogram of body weight.

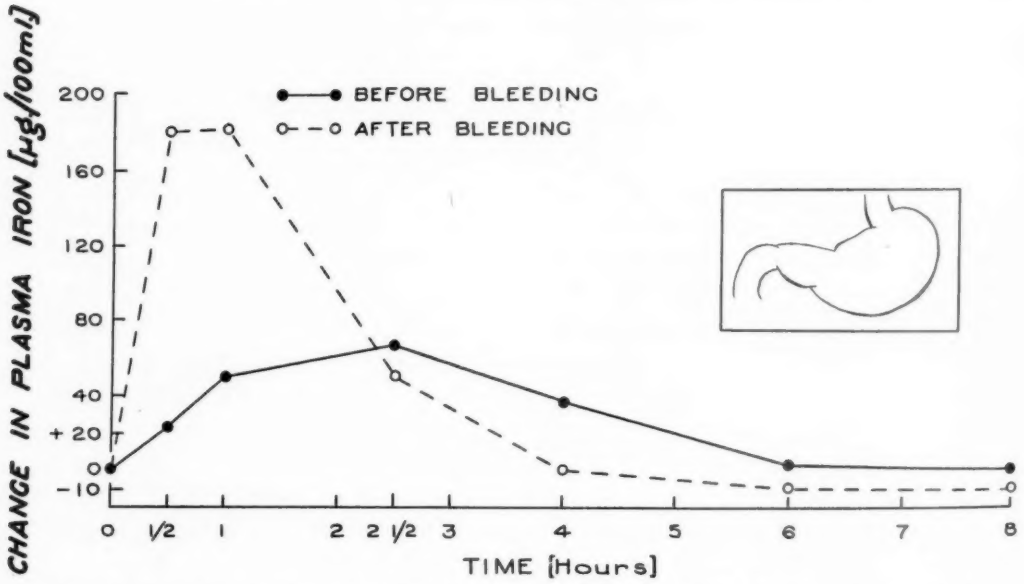

Fig. 2.—Graph showing the effect of iron depletion on a normal dog. Plasma iron levels following oral administration of 2 mg. of iron per kilogram of body weight are shown.

The results of the study of iron absorption in normal and in gastrectomized animals depleted of iron by repeated bleeding is shown in Figs. 2, 3, and 4 and in Table I. In normal dogs the increase in plasma iron following

oral administration of iron is definitely greater following iron depletion than it was before iron depletion. The dog with the subtotal gastrectomy was also able to increase its absorption of iron following depletion of its iron reserves (Fig. 3). Absorption of iron in a totally gastrectomized dog before and after depletion of iron is shown graphically in Fig. 4. In contrast to the normal or

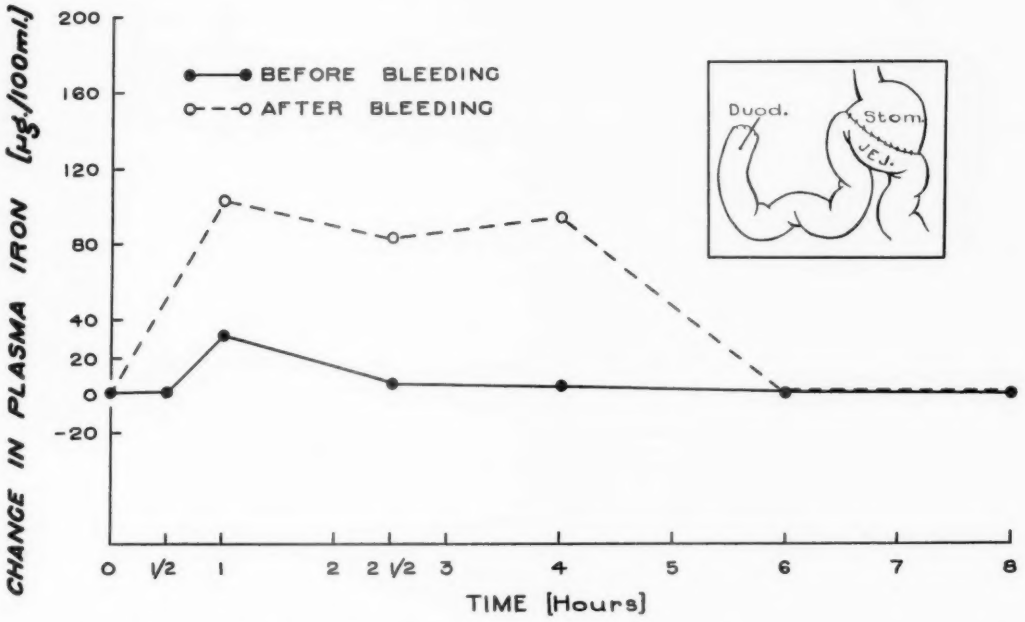

Fig. 3.—Effect of iron depletion on a dog with a subtotal gastrectomy. Plasma iron levels following oral administration of 2 mg. of iron per kilogram of body weight are shown on the graph.

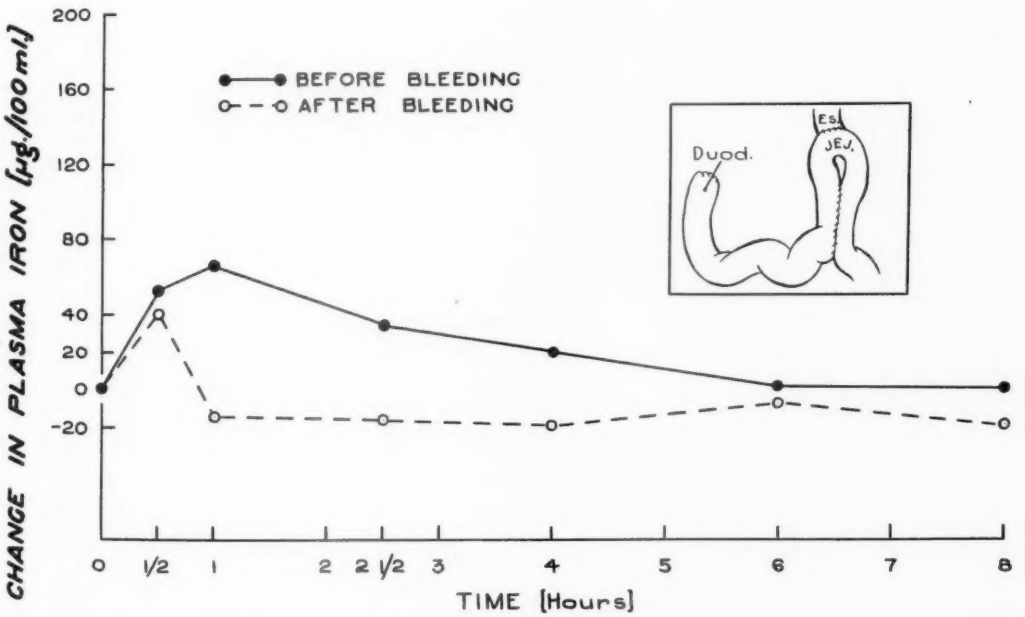

Fig. 4.—Effect of iron depletion on a dog with a total gastrectomy. Plasma iron levels following oral administration of 2 mg. of iron per kilogram of body weight are shown.

the subtotally gastrectomized dog, the absorption of iron following the oral administration of a test dose was in each experiment less after iron depletion than before.

TABLE I. IRON ABSORPTION BEFORE AND AFTER DEPLETION OF IRON STORES

TYPE OF ANIMAL	PLASMA IRON LEVELS (μG./100 ML.)						
	FASTING	AFTER ADMINISTRATION OF IRON (EXPRESSED AS DIFFERENCES FROM FASTING LEVELS IN HOURS)					
		½	1	2½	4	6	8
Normal dogs							
No. 11 before bleeding	17	23	50	66	36	3	1
after bleeding	30	180	181	50	0	−10	−10
No. 120 before bleeding	67	16	16	59	16	16	−50
after bleeding	43	65	99	92	99	0	0
Dog with subtotal gastrectomy							
No. 21 before bleeding	47	1	31	5	4	0	0
after bleeding	57	53	103	83	93	0	0
Dogs with total gastrectomy							
No. 46 before bleeding	53	133	158	130	107	57	7
after bleeding	43	14	0	−1	2	44	10
No. 56 before bleeding	21	92	46	52	2	34	9
after bleeding	33	12	−23	−10	−23	−15	−20
No. 90 before bleeding	51	53	66	34	20	11	11
after bleeding	36	41	−14	−16	−19	−8	−19
No. 100 before bleeding	62	141	108	85	111	104	62
after bleeding	19	68	51	39	31	48	13

Experiment No. 2. A Comparison of the Amounts of Hemoglobin that Must Be Removed to Maintain Anemia in Normal and in Gastrectomized Dogs.—

Method: The capacity of normal and gastrectomized dogs to regenerate hemoglobin during a period when no supplemental iron therapy was received was compared. For this purpose, the total quantity of hemoglobin removed from each dog during the preceding experiment on iron absorption (Experiment No. 1) was measured. The results are recorded as grams of hemoglobin per kilogram of body weight per day.

Results: In Table II the amounts of hemoglobin that had to be removed from each animal for the production and maintenance of anemia are shown. It is apparent that the largest amount of blood had to be removed from normal

TABLE II. AMOUNT OF HEMOGLOBIN REMOVED FROM DOGS DURING IRON DEPLETION STUDY TO MAINTAIN ANEMIA
(Grams/Kilogram Body Weight/Day)

TYPE OF ANIMAL	AMOUNT OF HEMOGLOBIN REMOVED
Normal dogs	
No. 11	0.69
No. 120	0.45
Dog with subtotal gastrectomy	
No. 21	0.11
Dogs with total gastrectomy	
No. 46	0.049
No. 56	0.093
No. 90	0.300
No. 100	0.170

dogs while removal of much smaller amounts sufficed to maintain anemia in gastrectomized dogs. This may be due to the fact that all of the dogs with total gastrectomy, as well as the dog with a subtotal gastrectomy, had lower rates of hemoglobin regeneration than did normal animals. In fact, the gastrectomized dog with the best ability to regenerate hemoglobin still produced only two-thirds as much hemoglobin as did the normal dog with the poorest hemoglobin regeneration. Regeneration of hemoglobin in the gastrectomized dog with the poorest hemoglobin regeneration rate was only one-ninth that of the corresponding normal dog.

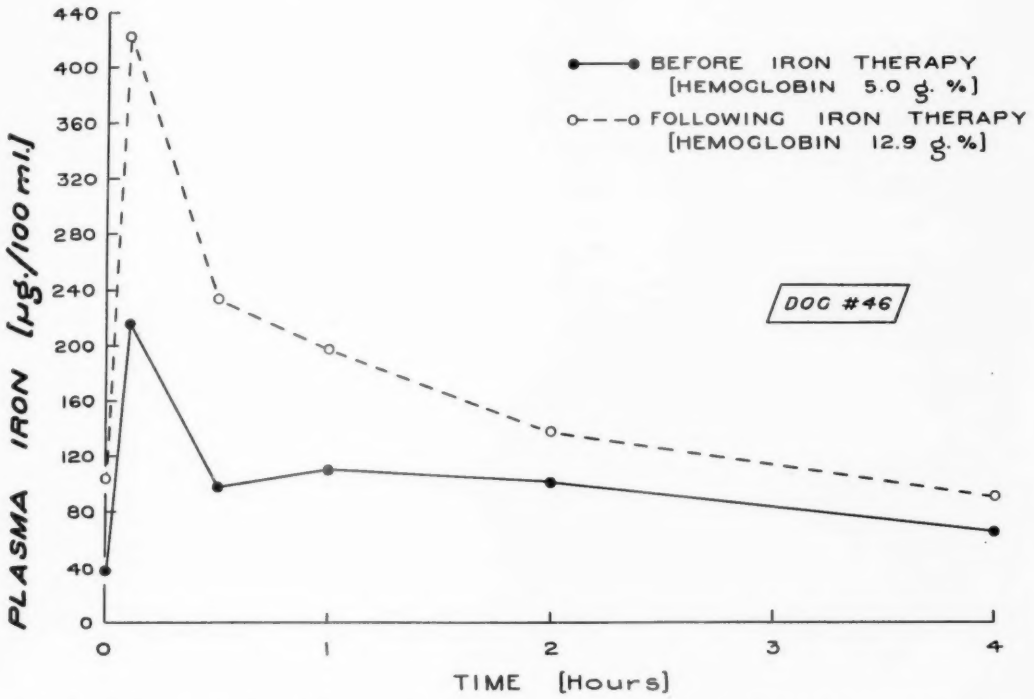

Fig. 5.—Intravenous iron tolerance test before and after regeneration of hemoglobin in a totally gastrectomized dog.

Experiment No. 3. The Utilization of Absorbed Iron in Gastrectomized Dogs.—Although the impaired capacity for regeneration of hemoglobin which was found in gastrectomized dogs was probably, at least in part, due to diminished absorption of iron from the intestine, the possibility that utilization of absorbed iron was inadequate in gastrectomized dogs also had to be considered. To investigate this latter possibility the utilization of iron was studied by intravenous iron tolerance tests.

Method: A dose of 4 mg. of elemental iron was given intravenously to a totally gastrectomized dog and samples of blood for analysis of the plasma iron were drawn at intervals of 5, 30, 60, 180, and 240 minutes.

Results: Fig. 5 shows the results of intravenous tolerance tests in the totally gastrectomized dog, first following depletion of his iron stores by bleeding, and later following intensive therapy with intravenous saccharated iron oxide.

(As a result of iron therapy the hemoglobin had risen to 13 Gm. per cent and the dog's iron stores presumably were largely replaced.) The plasma iron levels in the first intravenous iron tolerance test revealed a sharp rise at 5 minutes and a sharp decline by 30 minutes. The second iron tolerance test, which followed the intravenous iron therapy, showed not only a sharp rise to even higher levels within 5 minutes, but the return to normal levels was considerably delayed. The slower disappearance of iron from the plasma is interpreted as being due to partial saturation of iron stores as a result of the intravenous iron therapy.

Experiment No. 4. The Effect of Oral as Compared to Intravenous Iron Therapy on Regeneration of Hemoglobin.—Further information on the ability of the blood-forming organs in gastrectomized dogs to assimilate iron and to produce hemoglobin for newly synthesized erythrocytes was sought by a comparative study of the effects on hemoglobin regeneration of orally as compared to intravenously administered iron.

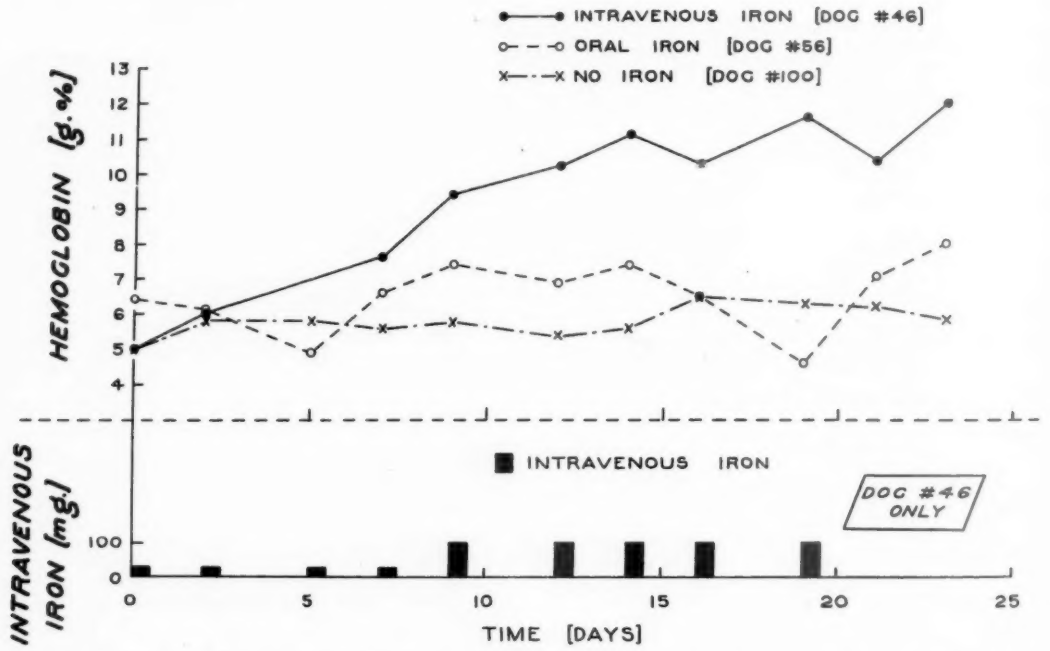

Fig. 6.—The effect of the route of administration of iron on the regeneration of hemoglobin in totally gastrectomized dogs.

Method: Three totally gastrectomized dogs that had been previously made anemic were used for this study. The initial hemoglobin levels varied from 5 to 6.5 Gm. per cent. One animal received saccharated iron oxide 3 times a week intravenously, a second received 300 mg. of ferrous gluconate daily by mouth, and a third received no iron therapy.

Results: The effect of the route of administration of iron on the regeneration of hemoglobin in totally gastrectomized dogs is shown in Fig. 6. Dog No. 46 received saccharated iron oxide intravenously in the amounts shown on the

graph. Dog No. 56 received 300 mg. of ferrous gluconate by mouth; Dog No. 100 had no iron therapy. As indicated on the graph, Dog No. 46 had a good response to treatment with intravenous iron, attaining a hemoglobin concentration that was almost normal in 3 weeks. Dog No. 56 had a poor response to oral iron therapy, and after 3 weeks this animal was still very anemic. Dog No. 100, maintained on the usual kennel ration without any iron replacement, showed no significant changes in its hemoglobin level.

The results of these experiments indicate that the iron deficiency anemia of the gastrectomized dog was due to impaired absorption of iron, because the utilization of iron apparently was entirely normal when given by the parenteral route.

DISCUSSION

The absorption of iron in totally gastrectomized dogs that have not been depleted of iron reserves does not differ significantly from that of normal dogs. However, the results of a study of iron absorption would be expected to differ according to the status of the iron stores of the patient at the time the test was performed because the individual with an adequate reserve of iron needs to absorb, and usually does absorb, only a small percentage of the iron administered. Therefore, a proper test of iron absorption requires study under conditions where increased absorption of iron is necessary. This is most easily done experimentally by depleting the reserves of iron by bleeding or by studies of iron absorption in patients who have an iron-deficiency anemia.

The findings of this study confirm the observation that the normal and subtotally gastrectomized dogs were able to increase the absorption of iron under such circumstances. However, totally gastrectomized dogs not only failed to compensate for their depleted iron stores by increasing iron absorption, but, in all of the 4 animals studied following total gastrectomy, the absorption of iron after a period of iron depletion was actually decreased. The reasons for the decreased absorption of iron under these circumstances are not apparent.

SUMMARY

The ability of normal and gastrectomized dogs to absorb and utilize iron has been studied.

Oral iron tolerance tests revealed essentially no difference between normal and gastrectomized dogs in the nonanemic state. However, in the anemic state, otherwise normal dogs demonstrated an increased absorption of iron whereas totally gastrectomized dogs failed to do so.

Considerably less hemoglobin had to be removed from gastrectomized dogs than from normal dogs to maintain anemia.

An anemic totally gastrectomized dog made a rapid recovery with intravenous iron therapy, whereas a similar totally gastrectomized animal had a delayed and poor response to oral iron therapy.

These experiments are presented as evidence that impaired absorption of iron is a consequence of total gastrectomy and that this is a major cause of the iron-deficiency anemia which may occur after gastrectomy.

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PARADOXICAL MOTION OF THE ABDOMINAL WALL IN RUPTURE OF THE DIAPHRAGM

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DURING the past 4 months 3 patients with ruptured diaphragms were seen who manifested an unusual motion of the abdominal wall with respiration. This consisted of a paradoxical motion of the ipsilateral upper abdominal wall. This unusual motion is caused by a paradoxically moving ruptured diaphragm.

CASE REPORTS

CASE 1.—B. B., a 57-year-old white man, was hospitalized after being hit by an automobile. He suffered multiple injuries consisting of fractures of the right tibia and fibula, supracondylar fracture of the left femur, fractures of the left superior pubic ramus, bimalleolar fractures of the left ankle, anterior dislocation of the left humerus with complete avulsion of the coronoid process, multiple lacerations, contusion of the small intestines, laceration of the liver, and ruptured left diaphragm. The following findings were of particular interest. The breath sounds were diminished over the left upper chest and were absent below the level of the fourth rib anteriorly. Peristaltic sounds were heard in the left axilla and as high as the level of the third intercostal space anteriorly. The left upper quadrant of the abdomen was unusually scaphoid. A marked paradoxical motion of the left upper quadrant of the abdomen was first noted in the admitting room (by W. H. K.). X-ray of the chest showed abdominal viscera up to the level of the fourth rib anteriorly (Fig. 1). At operation one-third of the pleural cavity was occupied by the stomach, spleen, transverse and proximal descending colon, and small intestines. There were 2 contused areas of small intestines. A 3 cm. cleft was palpated on the inferior aspect of the right lobe of the liver. There was a large rent in the left diaphragm extending 0.5 cm. from the esophageal hiatus to within 2 cm. of the chest wall at the midaxillary line. The posterior three-fifths of the diaphragm was paralyzed while the anterior two-fifths descended feebly with inspiration. A piece of gel foam soaked in thrombin was placed over the cleft in the liver. The diaphragm was repaired with interrupted 2-0 cotton sutures. Additional procedures consisted of repair of the lacerations and fractures. During the immediate postoperative period, the patient manifested a much lesser degree of paradoxical motion of the left upper quadrant of the abdomen.

CASE 2.—M. T., a 61-year-old white man, was hospitalized after being hit by an automobile. He suffered multiple injuries consisting of cerebral contusion, fracture of the right twelfth rib, fractures of the left superior and inferior pubic rami, fracture of the right superior pubic ramus, fractures of the left tibia and fibula, bimalleolar fractures of the right ankle, multiple lacerations, ruptured liver, ruptured right diaphragm, lacerations

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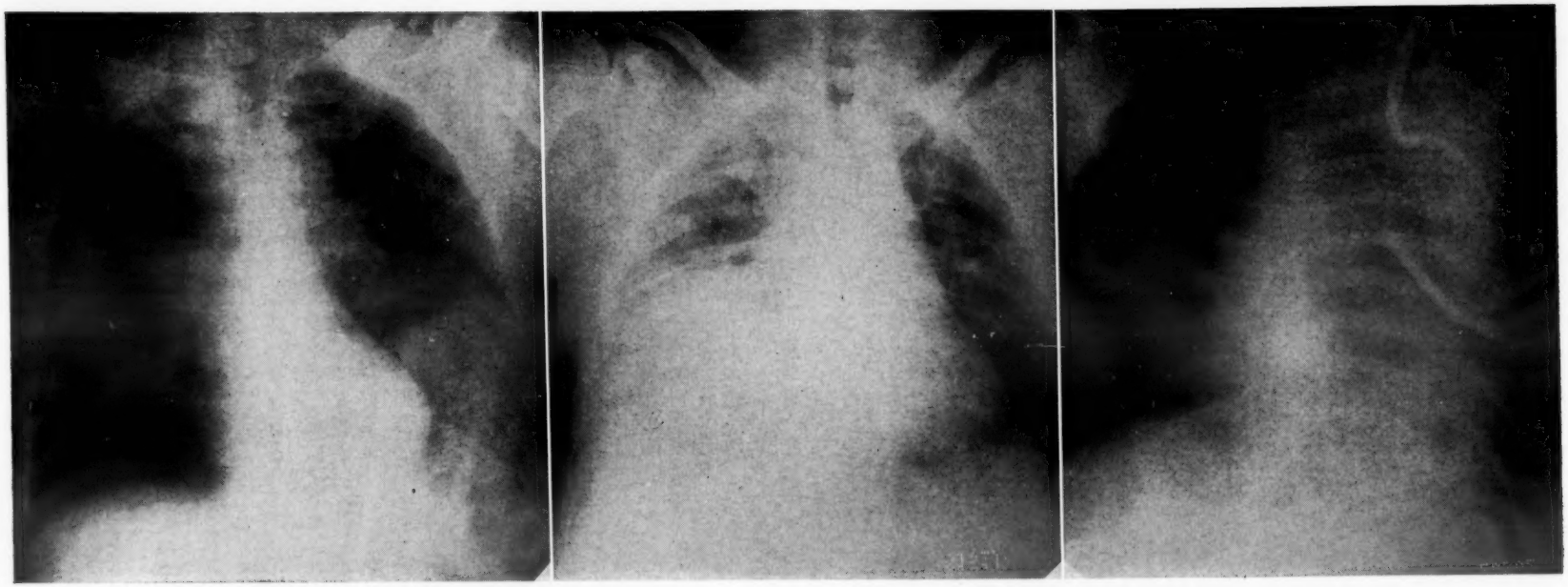

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Rupture of left diaphragm with abdominal viscera in left pleural cavity.
Fig. 2.—Rupture of right diaphragm. At autopsy the pleural cavity contained 1,000 ml. of blood and the upper half of a lacerated liver.
Fig. 3.—Rupture of left diaphragm and spleen with hemothorax.

of both kidneys, and perforation of the small bowel. On examination of the abdomen, a slight paradoxical motion of the right upper quadrant was noted. X-ray showed a homogeneous density in the lower half of the right chest (Fig. 2). The lacerations were repaired and the fractures of the lower extremities were immobilized. The patient was observed for possible intra-abdominal injuries and was scheduled for celiotomy 2 days after admission. However, he expired before this was accomplished. At autopsy there was a large stellate rupture of the right leaf of the diaphragm. The right pleural cavity contained approximately 1,000 ml. of blood and the upper half of a severely lacerated liver. There was a perforation of the small bowel with generalized purulent peritonitis.

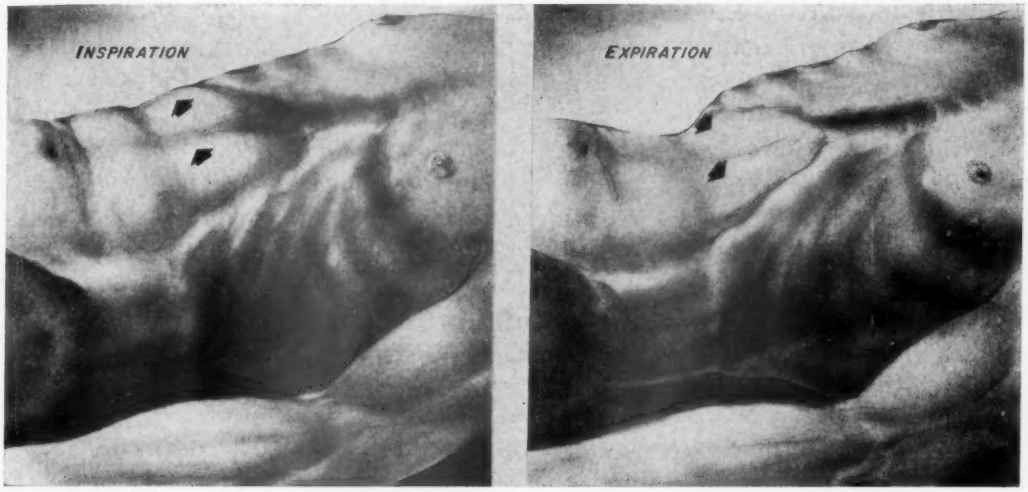

Fig. 4.—Normal motion of the upper abdomen during respiration.

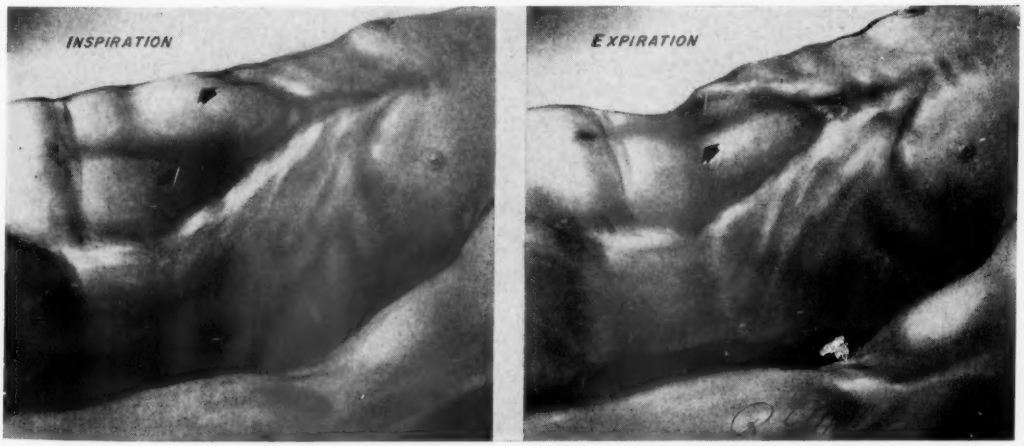

Fig. 5.—Paradoxical motion of the left upper quadrant of the abdomen with rupture of the left diaphragm.

CASE 3.—D. A., a 31-year-old white man, was hospitalized after being thrown out of an automobile. Because of a large left hemothorax and a suspected ruptured spleen, a left thoracotomy was performed (Fig. 3). One-fourth of the pleural cavity was occupied by the stomach, spleen, and transverse colon. There was a large rent in the diaphragm extending from the esophagus to within 5 cm. of the chest wall at the mid-axillary line. The posterior two-fifths of the diaphragm was paralyzed while the anterior three-fifths

descended with inspiration. The spleen was removed and the diaphragm repaired with interrupted 2-0 cotton sutures. Preoperatively a slight paradoxical motion of the left upper quadrant of the abdomen was noted.

COMMENTS

Rupture of the diaphragm is usually diagnosed by an x-ray examination of the chest. Confirmatory signs due to abdominal viscera in the pleural cavity may be present. Solid viscera may cause a decrease in resonance and breath sounds. Hollow viscera may be accompanied by tympany and peristaltic sounds in the chest. A paradoxical motion of the corresponding upper quadrant of the abdomen may be present. Normal respiratory movements are produced by the diaphragm and thoracic cage. The abdominal muscles play a passive role in inspiration. During inspiration the thoracic cage expands and the diaphragm descends causing the upper abdomen to distend passively (Fig. 4). These movements are reversed in expiration. When the diaphragm is ruptured the denervated portion moves in a paradoxical manner. During inspiration it is displaced into the pleural cavity by the negative intrapleural pressure. As a consequence, the ipsilateral upper abdominal wall is retracted during inspiration and distended during expiration (Fig. 5). This motion appears to be accentuated when the upper abdomen is scaphoid as a result of visceral displacement into the pleural cavity.

CONCLUSION

An unusual physical finding in 3 cases of ruptured diaphragm is described. This consists of a paradoxical motion of the ipsilateral upper quadrant of the abdomen. This motion is caused by a paradoxically moving ruptured diaphragm. The occurrence of paradoxical motion of an upper abdominal quadrant after blunt abdominal trauma is diagnostic of a ruptured diaphragm.

THE EFFECT OF COMPLETE EXCLUSION OF THE STOMACH ON FAT AND NITROGEN ABSORPTION

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IT HAS generally been noted that nutrition in patients following total gastrectomy is poor; these individuals rarely gain weight or even maintain their preoperative weight. The percentage of fat and nitrogen absorbed by gastrectomized patients and dogs is less than that absorbed by normal subjects.[1-4] These observations are true in varying degrees, regardless of the type of surgical reconstitution.[2] Nutrition, as measured by weight gain and fat and nitrogen utilization studies, is more satisfactory in patients and animals with a remaining remnant of stomach. This suggests that the stomach, in addition to its usual role in digestion, has perhaps an endocrine role in promoting fat and/or nitrogen absorption from the gastrointestinal tract or that the presence of gastric juice in the small intestine might facilitate absorption.

It is the purpose of this investigation to attempt delineation of such a mechanism, if it exists, by determining the absorption of fat and nitrogen in dogs during 3 consecutive experimental situations: (1) in which the entire stomach is excluded by a Roux Y esophagojejunostomy, (2) in which the secretions of the completely isolated stomach are drained to the exterior through a gastric cannula, and (3) in which the stomach is removed from the animal.

MATERIALS AND METHODS

Five adult mongrel dogs weighing 13 to 21 Kg. each, were used for these experiments. The first stage in the series of operations consisted of transection of the esophagus just above the cardiac sphincter and inversion of the cardiac orifice of the stomach. The jejunum was transected 20 cm. beyond the ligament of Treitz, and the segment of the jejunum distal to the transection was brought up to the esophagus. The proximal segment of jejunum was drained into the jejunum 20 cm. distal to the esophagojejunostomy, completing the Roux Y procedure. The stomach was entirely bypassed, but its secretions emptied through the duodenum into the digestive current.

The second stage consisted of transecting the duodenum just distal to the pylorus, inserting a stainless steel gastric cannula for drainage, and closing

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both ends of the transected duodenum. The stomach was now completely isolated from the alimentary canal, and its secretions were diverted to the exterior.

The third stage consisted of removing the isolated stomach from the animal.

Following complete recovery from each phase of the experiments, the animals were offered a diet consisting of 460 Gm. of prepared canned dog food (Friskies) with 37.5 Gm. of olive oil added; in addition, 0 to 20 Gm. of a methylcellulose preparation (Alphacel) was mixed with the diet as necessary to control and prevent diarrhea. The animals were also given 200 c.c. of evaporated milk daily. The total daily diet offered was 76.6 Gm. of fat and 5.22 of nitrogen. Sodium chloride was added to the diet, as necessary, during the second stage to replace electrolyte loss from gastric juice drainage. Each day the uneaten portion of the diet was removed from the animal's cage and weighed. Feces were collected for three 4-day periods during each part of the experiment. Each 4-day pool was homogenized and an aliquot was analyzed for fat and nitrogen content.

Analysis for nitrogen was done by the micro-Kjeldahl method and total fat determinations were done by the ether extraction method. The results are expressed in terms of percentage of ingested fat and nitrogen retained by the animals.

RESULTS*

Fig. 1 demonstrates the progressive weight loss seen in all of the dogs. Removal of the stomach did not cause any greater rate of weight loss in any of the dogs; in fact, 2 of the 3 dogs followed for over 2 weeks after total gastrectomy had essentially no weight loss. Fig. 2 presents the data concerned with percentage of ingested fat retained by these animals during the different stages of the experiment. Each bargraph represents a 12-day period on nutritional balance.

It is immediately apparent that the initial operation of complete gastric exclusion produced a moderately severe steatorrhea in all 5 animals. Normal dogs retain 90 to 95 per cent of ingested fat, while during the first stage of the present experiment the 5 animals retained only 48 to 62 per cent of ingested fat.

Following the second stage operative procedure with division of the pylorus and external drainage of gastric secretion, there was no significant change in fat absorption in any of the 5 animals; 3 showed a slight decrease and 2 a slight increase. After complete removal of the isolated stomach, there was again no significant change in fat absorption in any of the 3 animals adequately studied; 2 showed a slight increase in fat absorption and the third a minor decrease.

The results of the balance studies in regard to the absorption of nitrogen from the diet are presented in Fig. 3. One animal (Dog No. 4) showed a

*Two of the 5 experimental animals expired within a week after total gastrectomy, and, hence, data for the third stage are incomplete.

moderate decrease in nitrogen retention after the second stage of operation, but, with this single exception, neither the second nor the third stage was followed by any significant change in the defect of nitrogen absorption produced by the initial operative procedure.

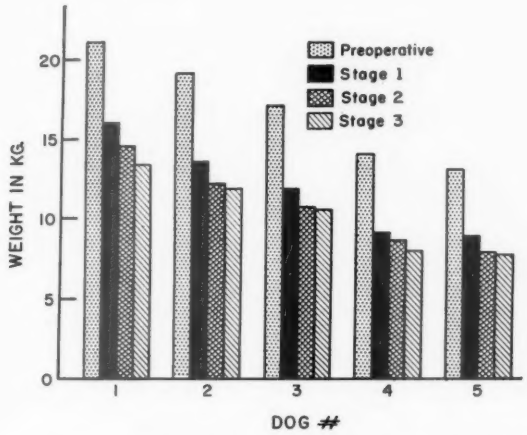

Fig. 1.—The effect of complete exclusion, isolation, and resection of the stomach on body weight.

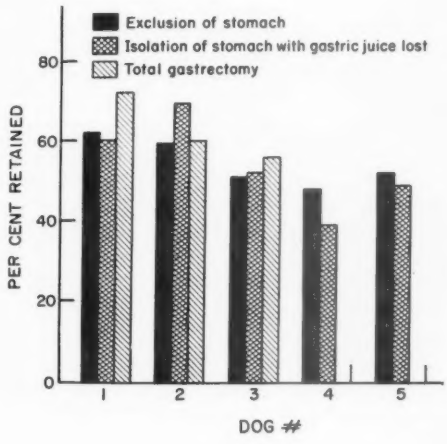

Fig. 2.

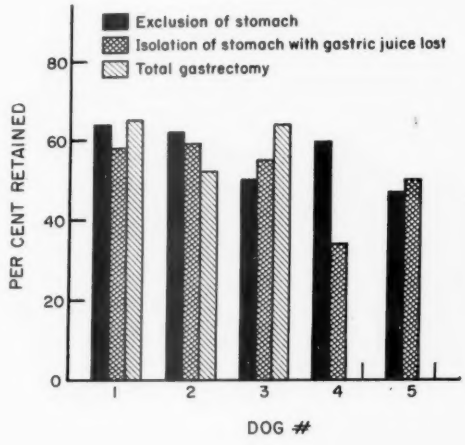

Fig. 3.

Fig. 2.—The absorption of fat in dogs subjected successively to exclusion of stomach, isolation of stomach with gastric juice lost, and total gastrectomy.

Fig. 3.—The absorption of nitrogen in dogs subjected successively to exclusion of stomach, isolation of stomach with gastric juice lost, and total gastrectomy.

DISCUSSION AND SUMMARY

Complete exclusion of the stomach from intestinal continuity by means of a Roux Y esophagojejunostomy produced a moderately severe defect in the absorption of ingested fat and nitrogen in each of the 5 dogs utilized in this study. This nutritive defect was not altered by division of the pylorus and total loss of gastric secretions to the exterior. This would render it unlikely that the entrance of gastric juice into the small intestine influences the digestive processes at this level. Following total gastrectomy, there was again

no significant alteration in the absorption of nitrogen and fat. This observation makes it seem unlikely that the stomach exercises any endocrine influence over the digestive processes in the small intestine.

All animals lost weight progressively throughout the 3 stages of the experiment. This loss tended to decelerate during the second and third stages, and this observation tends to reinforce the conclusion that the excluded or isolated stomach exerts no beneficial effect on digestion or absorption.

We are grateful for the valuable technical assistance of Mrs. Genevieve Armstrong in performing the many fat and nitrogen analyses.

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CAUDAL PANCREATOJEJUNOSTOMY IN THE MANAGEMENT OF CHRONIC RELAPSING PANCREATITIS

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THE surgical procedures employed in attempting to alleviate symptoms of chronic pancreatitis have, in most instances, been designed to alter physiologic processes thought to be of etiologic importance, despite the lack of definitive evidence supporting the theories of pathogenesis. A concept which has gained increasing popularity in recent years postulates that obstruction of the pancreatic ducts is a factor in the pathogenesis of this disease; a concept supported by the studies of Priesel,[10] as well as those of Rich and Duff.[21] Based on this concept, new operations have been devised. In 1946 Cattell[2] proposed anastomosis of the duct of Wirsung in continuity to the upper jejunum, but Warren[13] in 1955 reported that this procedure had been used only occasionally and advocated dilatation of strictured areas as the preferred method of treatment. In 1954 DuVal[3] and Zollinger[15] independently suggested resection of the tail of the pancreas and caudal pancreatojejunostomy for the management of this problem. This procedure should allow drainage of the pancreas in a retrograde manner and, if obstruction were the problem, should eliminate the difficulty. Link's[8] report of a patient in whom the development of a caudal pancreatocutaneous fistula resulted in improvement over a period of many years indicated that this concept might be valid.

Believing that caudal decompression would more likely produce lasting benefit than would simple dilatation of areas which could readily stricture again, the evaluation of this procedure was undertaken approximately 2 years ago. During the intervening period, caudal pancreatojejunostomy has been performed in 9 patients. With one exception, each had a normal biliary tract. This patient had gallstones, but he was a confirmed alcoholic, and his attacks of pancreatitis were associated with his alcoholic sprees. Six patients were alcoholics; another stated that he used alcohol in moderation. It is in patients without biliary tract disease and particularly in those with chronic alcoholism, that the problem of relapsing pancreatitis is particularly difficult and in which new procedures need to be evaluated.

CASE REPORTS

CASE 1.—A 44-year-old Negro man was admitted to the Veterans Administration Hospital, Houston, Texas, on April 6, 1955, complaining of abdominal pain of 2 weeks'

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duration. Past history revealed that a diagnosis of pancreatitis had been made elsewhere in 1953, and surgical therapy, consisting of a cholecystectomy, common duct exploration with drainage, and sphincterotomy, had been performed.

He was treated nonoperatively with a presumptive diagnosis of acute pancreatitis, although the serum amylase concentration was within normal limits. Pain gradually improved so that he was discharged 2 weeks later, roentgenographic evaluation of the gastrointestinal tract having failed to disclose any disease.

He was readmitted on May 12, 1955, with a recurrence of symptoms; the serum amylase was elevated. Abdominal exploration revealed a normal common duct and confirmed the surgical absence of the gall bladder. The entire pancreas was hard and nodular. The tail of the pancreas was excised without removing the spleen. The pancreatic duct was found to be dilated and juice flowed freely from its cut end. A retrocolic end-to-end pancreatojejunostomy Roux Y was performed (Fig. 1). The postoperative course was uneventful. He remained asymptomatic until July 22, 1957, when he was readmitted with a recurrence of symptoms. The serum amylase concentration was elevated.

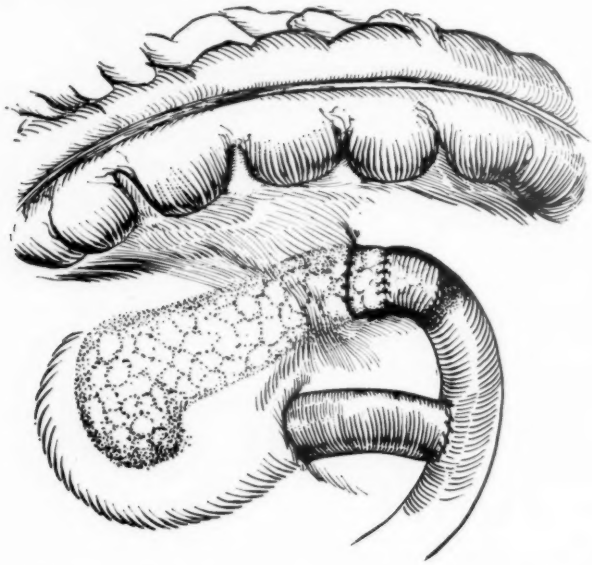

Fig. 1.—Diagram to illustrate technique of end-to-end caudal pancreatojejunostomy. The anastomosis was placed in the retrocolic position, and the jejunal limb measured 18 inches in length.

CASE 2.—A 29-year-old white man was admitted to the Veterans Administration Hospital, Houston, Texas, in May, 1954, with complaints of abdominal pain. Examination led to a presumptive diagnosis of active duodenal ulcer and his symptoms subsided under conservative therapy. He was readmitted in June, 1954, stating that he had been essentially asymptomatic until 2 days prior to admission when abdominal pain had recurred, accompanied by nausea and vomiting. On examination the abdomen was found to be rigid. The serum amylase concentration was elevated. Operation was performed on the night of admission with a preoperative diagnosis of perforated duodenal ulcer, but no ulcer was found. The operative diagnosis was severe hemorrhagic pancreatitis. He experienced a difficult postoperative course marked by persistent drainage from the abdomen, delirium tremens, and a chronic febrile course, with recurrent elevations of the serum amylase concentration, but he gradually improved and was discharged 2 months after operation.

During the ensuing year, this patient was readmitted 3 times for episodes of acute pancreatitis, with elevated serum amylase concentrations on each admission. On 2 occasions he had delirium tremens.

He was again admitted because of recurrence of his abdominal complaints on March 12, 1956. The serum amylase concentration was elevated. After 3 weeks, during which time he failed to respond to conservative therapy, abdominal exploration was performed. The entire pancreas was enlarged, hard, and nodular. The tail of the pancreas and the spleen were excised. The pancreatic duct was found to be dilated and juice flowed freely from it. When a pancreatogram, performed on the operating table, failed to show the entrance of the dye into the duodenum, a caudal pancreatojejunostomy Roux Y was performed. A duodenotomy was then performed to inspect the ampulla of Vater, and a sphincterotomy was performed. Bile flowed freely from the sphincter, and no intrinsic biliary pathology was discerned. The opening of the pancreatic duct was not identified. The immediate postoperative course was uncomplicated, and he was asymptomatic when discharged on May 1, 1956. However, within the next 7 months he was readmitted on 2 occasions with attacks of pancreatitis. Each attack was preceded by ingestion of alcohol.

CASE 3.—This 26-year-old Negro man was first admitted to the Veterans Administration Hospital, Houston, Texas, in December, 1953, complaining of upper abdominal pain with radiation to the back. Examination revealed abdominal tenderness, and laboratory examinations were within normal limits except for an elevated serum amylase concentration. During the next 3 years, the patient had 9 admissions for similar complaints, and on each admission the serum amylase concentration was found to be elevated. Roentgenographic examinations of the gastrointestinal tract and of the biliary tree were within normal limits.

He was readmitted because of recurrent pain on Dec. 16, 1956. Treatment with intravenous fluids, atropine, and sedation was instituted and, as symptoms subsided, a low fat diet was prescribed. Surgical intervention was recommended, but was deferred until Jan. 16, 1957, to allow resolution of the inflammatory process. On this date a laparotomy was performed. The common duct, gall bladder, stomach, and duodenum were normal. There was marked induration of the pancreas at the head and tail with surrounding adhesions. The secretions within the duct were under pressure and contained small solid particles. The duct was probed and found to be constricted just proximal to the point of transection and in the head. A pancreatogram was performed on the operating table, revealing 2 constrictions of the pancreatic duct, one 3 cm. from the ampulla and one in the mid-portion of the body of the pancreas, but dye passed slowly into the duodenum. An end-to-end pancreatojejunostomy Roux Y was performed. The postoperative course was complicated by a mild wound infection.

The patient was discharged on Feb. 19, 1957, but returned to the hospital in March, 1957, complaining of mild upper abdominal pain. Examination revealed that he was severely intoxicated; no clinical or enzymatic evidence of pancreatitis could be found. He was discharged upon recovery from alcoholism only to return 2 months later complaining of epigastric pain with radiation to the back. He denied ingestion of alcohol since his previous discharge. Examination revealed a temperature of 101° F. and epigastric tenderness. The serum amylase concentration was elevated.

CASE 4.—A 42-year-old white man was admitted to the Veterans Administration Hospital Houston, Texas, on March 7, 1956, with a 10-year history of intermittent episodes of severe upper abdominal pain and associated vomiting. At times the symptoms appeared to be relieved by the ingestion of food and alkali. The most recent episode was of 3 weeks' duration.

The serum amylase concentration was elevated. Hepatic function tests were within normal limits. Roentgenographic studies of the stomach, small bowel, and colon were within normal limits, and 2 separate studies of the gall bladder showed normal function without stones. However, a flat plate of the abdomen demonstrated calcification in the upper mid-abdomen consistent with a diagnosis of pancreatic calculi. A diagnosis of chronic relapsing pancreatitis was established.

The abdominal pain persisted despite nonoperative therapy; therefore, on April 16, 1956, abdominal exploration was performed. There was gelatinous edema about the head of the pancreas and in the retroperitoneal space. There were 5 or 6 small cystic areas in the head of the pancreas, but no single cyst was larger than 1 cm. in diameter. The head, body, and tail of the pancreas were firm and nodular. When a resection of the tail of the pancreas was performed, the pancreatic duct was found to be dilated; juice spurted from the cut end of the duct. A Roux Y distal pancreatoenterostomy was performed and was followed by an uneventful postoperative course.

During the ensuing 6 months, he was readmitted with 3 attacks of abdominal pain, which subsided without specific therapy. The serum amylase concentration was elevated with 2 of these attacks.

His last admission was on Dec. 5, 1956, when he was readmitted for similar symptoms. He had lost 15 pounds in weight. A gastrointestinal series at this time showed extensive deformity of the first and second portions of the duodenum, presumably due to surrounding inflammation in the head of the pancreas. On Jan. 8, 1957, his abdominal discomfort increased and jaundice became clinically evident. The serum bilirubin was 3.4 mg. per cent, alkaline phosphatase 41.2 Bodansky units, cephalin flocculation negative, thymol turbidity 1 unit, and prothrombin time 100 per cent. Nasogastric suction was instituted and he was placed on a conservative regimen in hopes that the inflammatory process in the pancreas would subside, but the jaundice persisted, with the serum bilirubin rising to 4.6 mg. per cent. On Jan. 13, 1957, the abdominal pain became much more severe and a spiking temperature developed, rising to 103° F. daily. Two days later the gall bladder became palpable in the right upper quadrant, and on Jan. 17, 1957, abdominal exploration was carried out. There was severe edema about the head of the pancreas, filling the entire retroperitoneal space in the right upper quadrant. The fundus of the gall bladder was markedly distended, but the common duct was involved in the inflammatory process and could not be specifically identified. The original plan of attack had been to perform a pancreatoduodenal resection, but the extreme retroperitoneal inflammatory reaction made satisfactory identification of important structures impossible. This approach was abandoned, therefore, and a cholecystojejunostomy was performed. The postoperative course was uneventful. His jaundice cleared by the sixth postoperative day, and he was discharged Feb. 12, 1957.

CASE 5.—A 35-year-old white woman was first admitted on May 13, 1955, to the Veterans Administration Hospital, Houston, Texas, stating that she had been in good health prior to Aug. 21, 1954, when she first suffered an acute attack of upper abdominal pain radiating directly posteriorly to the back, with associated nausea, vomiting, and fever. She was hospitalized at another institution with a diagnosis of acute cholecystitis and acute pancreatitis; the latter diagnosis was substantiated by an elevation of the serum amylase concentration. She was treated nonoperatively with relief of symptoms.

Thereafter, the patient had recurrent episodes of right upper quadrant and cramping abdominal pain with posterior radiation. She was admitted to this hospital because of persistence of symptoms. Physical examination and all laboratory and roentgenographic examinations were within normal limits. Because of the persistent abdominal pain, abdominal exploration was performed on May 27, 1955. The gall bladder was normal, as was the common duct; however, the entire pancreas was markedly indurated and swollen. A diagnosis of chronic pancreatitis was made, but no specific therapy was instituted.

She was readmitted to the hospital on March 22, 1956, stating that symptoms had recurred in January, 1956. Since that time right upper quadrant pain had persisted and had become progressively worse. Physical examination on this admission again revealed tenderness to palpation in the right upper quadrant and in the epigastrium. All previous laboratory examinations were repeated and again were within normal limits. Because of the proved attacks of pancreatitis in the past and the failure to identify any other cause for the abdominal pain, operation was performed on April 10, 1956. Examination of the entire abdomen was negative except for the pancreas which showed thickening in the

head compatible with the diagnosis of chronic pancreatitis. The tail and body of the pancreas were slightly indurated. An excision of the distal 4 cm. of the tail of the pancreas was performed, and an end-to-end pancreatojejunostomy accomplished to a Roux Y limb. The postoperative course was complicated by the development of thrombophlebitis in the left leg, but she was discharged from the hospital on May 12, 1956. She remained asymptomatic until November, 1956, when she experienced recurrence of right upper quadrant and epigastric pain similar to that which she had had preoperatively. During the ensuing month, similar episodes were experienced, but the serum amylase was not elevated on either occasion.

CASE 6.—A 38-year-old alcoholic white woman was first admitted to Grady Memorial Hospital, Atlanta, Georgia, on July 11, 1956, with complaints of constant aching epigastric pain of 3 years' duration. There was an associated weight loss. In November, 1955, she had been admitted to another hospital where roentgenographic examination had revealed calcification of the pancreas.

A conservative regimen failed to afford relief, and therefore a noncalculous gall bladder was removed and a sphincterotomy was performed. Symptoms recurred 3 weeks following operation.

At the time of this admission, symptoms continued unchanged; roentgenographic examinations again revealed pancreatic calcification, and a cholangiogram revealed a widely patent common duct. Other studies were within normal limits. Operation was performed on July 23, 1956. The pancreas was thickened and grossly diseased. The tail of the pancreas and the spleen were resected. When the pancreatic duct was probed, calcific areas were encountered. A pancreatogram was performed on the operating table, and an obstruction of the duct was noted in the head of the pancreas; consequently a pancreatojejunostomy Roux Y was performed. The immediate postoperative period was uneventful.

She was readmitted on Jan. 8, 1957, because of recurrent and persistent pain. The pain had recurred shortly after operation and had become more severe during the 3 weeks immediately prior to this admission. The serum amylase concentration was normal. However, the pain was typical of pancreatitis and occurred only with the consumption of large amounts of alcohol.

CASE 7.—A 33-year-old alcoholic Negro woman was hospitalized in Grady Memorial Hospital, Atlanta, Georgia, in March, 1957, with a history dating back to 1951 when she had first been seen in the emergency clinic with abdominal pain which followed the ingestion of alcohol. Between 1951 and 1957, she had had numerous attacks of pain and, on 3 occasions, was admitted to the hospital. The serum amylase concentration was elevated on each admission, while roentgenographic studies of the gall bladder and gastrointestinal tract were within normal limits. On March 14, 1957, abdominal exploration was performed. The biliary tree was normal. The pancreas was firm and nodular, showing small areas of fat necrosis with fibrosis and no calcification. An operative pancreatogram revealed a free flow of dye into the duodenum. Caudal pancreatectomy with pancreatojejunostomy Roux Y was performed, removing all of the pancreas to the left of the superior mesenteric artery. The spleen was left intact. The abdominal pain subsided on the fifth postoperative day, and she was discharged on the thirteenth postoperative day, having had an uneventful postoperative course.

She was last seen in May, 1957, at which time she was asymptomatic. During this time she had refrained from drinking alcohol.

CASE 8.—A 28-year-old alcoholic white man was first admitted to the Veterans Administration Hospital, Atlanta, Georgia, in July, 1954, complaining of abdominal pain, nausea, and vomiting of 3 weeks' duration. His past history revealed that he had experienced episodic bouts of epigastric and substernal pain for a number of years. The serum amylase concentration was elevated and the diagnosis of acute pancreatitis was established. Abdominal exploration was performed when he was readmitted with a recurrence

of symptoms and an elevated serum amylase concentration in October, 1954. The pathologic findings were those of chronic pancreatitis and chronic cholecystitis with cholelithiasis. Exploration of the common duct was negative. Sphincterotomy and T-tube drainage were performed. The T tube was removed 2 weeks postoperatively.

During the next 12 months symptoms recurred on several occasions. Therefore, on Jan. 13, 1956, the abdomen was again explored. The pancreas was found to be indurated, hard, and fibrotic. The pancreatic duct was cannulated with a polyethylene tube, and a pancreatogram revealed a free flow of dye into the duodenum. A caudal pancreatectomy with a pancreatojejunostomy Roux Y was performed. The postoperative course was uneventful. The patient was discharged on Jan. 21, 1956. Since discharge he has experienced several attacks of abdominal pain similar to those prior to operation, though less severe.

CASE 9.—A 60-year-old Negro man was first admitted to Jefferson Davis Hospital, Houston, Texas, in May, 1953, complaining of dull, constant epigastric pain which radiated posteriorly into the back. He stated that he took alcohol in moderation only. There was associated vomiting and weight loss of 22 pounds. At the time of admission, the serum amylase concentration was elevated, and a plain roentgenogram of the abdomen revealed pancreatic calculi. Other examinations, including roentgenographic studies of the biliary tract and upper gastrointestinal tract, were within normal limits. During the ensuing year he experienced 7 episodes of acute abdominal pain and was readmitted with this complaint in November, 1954, at which time the serum amylase concentration was elevated. The pancreatic stones were again demonstrated on a roentgenogram of the abdomen.

A recurrence of symptoms developed in April, 1955, and on this admission an elective laparotomy was performed. The gall bladder was normal. The pancreas was 3 times normal size, hard, and nodular. The tail of the pancreas was excised, at which time a dilated duct was identified, which was filled with thick, pasty material. A pancreatojejunostomy Roux Y was performed. The postoperative course was uneventful, and the patient was asymptomatic when last seen in May, 1956.

DISCUSSION

It is generally agreed that existing biliary tract disease should be eliminated as the first step in the surgical management of chronic pancreatitis, for patients with cholelithiasis or choledocholithiasis are likely to obtain symptomatic relief following surgical intervention. Patients in whom biliary tract disease does not exist have a much less favorable prognosis. The concept of intrapancreatic ductal obstruction might explain this discrepancy and, therefore, pancreatojejunostomy seems a logical procedure to use in these patients. A review of the literature resulted in the collection of only 57 patients in whom this procedure has been used.[3-7, 11, 13-15]

No mortality has been reported, nor have there been serious intra-abdominal complications; consequently, from a technical point, this is a safe procedure. The problem, however, concerns the long-term alleviation of symptoms of chronic relapsing pancreatitis. Many of the case reports fail to give information concerning long-term results. However, the data available are in general encouraging, as exemplified by those of DuVal who reported good results in 80 per cent of his 25 patients who had been followed 6 months to 3 years. Our experience does not follow this pattern, for 4 of our patients have already had definite recurrence of their disease, despite a very short follow-up period, and recurrent symptoms suggestive of pancreatitis have been noted in 3 additional patients (Table I).

TABLE I. SUMMARY OF DATA ON 9 PATIENTS WITH CHRONIC RELAPSING PANCREATITIS TREATED BY CAUDAL PANCREATOJEJUNOSTOMY

CASE NO.	AGE	SEX	DURATION OF SYMPTOMS (YEARS)	ALCOHOLISM	CALCIFICATION	PREVIOUS SURGERY		DUCTAL OBSTRUCTION	DURATION OF FOLLOW-UP (MONTHS)	RECURRENCE	
						CHOLECYSTECTOMY	SPHINCTEROTOMY			PROVED	SUSPECTED
1	44	M	2	0	0	+	+	+	27	+	0
2	29	M	2	+	0	0	0	+	8	+	0
3	26	M	3	+	0	0	0	+	6	+	0
4	42	M	10	0	+	0	0	+	10	+	0
5	35	F	2	+	0	0	0	0	10	0	+
6	38	F	3	+	+	+	+	+	7	0	+
7	33	F	6	+	0	0	0	0	2	0	0
8	28	M	"Several"	+	0	+	+	0	12	0	+
9	60	M	2	0	+	0	0	+	12	0	0

There is adequate clinical evidence to substantiate the diagnosis of chronic pancreatitis in each of our patients, and in each there is histologic confirmation. The only question to be raised is whether or not all patients were suitable candidates for the operation. DuVal originally suggested that the operation be used in patients in whom definite ductal obstruction could be demonstrated at operation, although this selection of patients was predicated upon theoretical grounds rather than an actual clinical experience. In fact, a review of the 25 patients on whom he reported follow-up results indicated that there was proved ductal obstruction in only 15; 4 had no obstruction and in 6 the duct was not specifically explored. The percentage of patients obtaining relief of symptoms was similar in each group. The pancreatic duct was explored in 6 of our patients, 4 of whom showed areas of obstruction, while 2 did not. Of the remaining 3 patients, there was presumptive evidence of ductal obstruction in 2 manifested by a markedly dilated duct containing juice under pressure, while in the third patient, the duct appeared normal in size and it was presumed that there was no obstruction. Each of the 4 patients with definite recurrence had ductal obstruction.

Four of our patients also represent failures of sphincterotomy, for 3 had had sphincterotomy prior to the performance of the pancreatojejunostomy, while the fourth had this operation performed concurrently.

In none of these patients was the disease limited to the tail or body of the pancreas. When the disease is anatomically limited to these areas, excision of the involved portion produces good results. In each of the patients herein reported, the excision of the tail of the pancreas was simply to facilitate pancreatojejunostomy and was not, in itself, felt to be of therapeutic value; for when the disease process involves the head of the gland, excisional therapy must, of necessity, be a subtotal pancreatoduodenectomy or a total pancreatectomy. In our opinion, a total pancreatectomy is not justified, because of the associated mortality and morbidity. Subtotal pancreatoduodenectomy, preserving enough of the pancreas to prevent diabetes, has been accomplished in recent years with a decreasing mortality rate, according to the reports of Warren[13] and Longmire,[9] and this procedure has given a high percentage of long-term good results. However, most surgeons report the mortality and morbidity following resection of the head of the pancreas to be higher than that following operative procedures of lesser magnitude. Therefore, it would appear that the use of resection procedures involving the head of the pancreas should be limited to those patients in whom less extensive procedures fail.

We agree with those who maintain that there is no one method of surgical therapy which is applicable to all patients with chronic relapsing pancreatitis. Each patient must be critically evaluated before surgery is advocated. In some, no operation will be indicated as attacks are mild and infrequent. When surgical intervention is necessary, a thorough exploration of the entire abdomen should be made to exclude other causes of symptoms. Specific and detailed examination of the biliary tree and the pancreatic ducts is mandatory. The choice of surgical procedures will then be predicated upon the findings in

the particular patient. The value of caudal pancreatojejunostomy cannot be accurately ascertained at this time. The good results reported by others indicate that this has some merit, but we are discouraged by the fact that in our experience recurrence of symptoms has occurred in those patients who theoretically should have been ideal candidates for operation. Attacks of pancreatitis were associated with episodes of alcoholic ingestion in many instances, and it is possible that in some patients alcoholism is a more important etiologic agent affecting recurrence than are the structural changes within the gland.

SUMMARY

A review of the literature has resulted in the collection of 57 patients with chronic pancreatitis treated by caudal pancreatojejunostomy. Follow-up data are not complete in all cases, but reports indicate good results in approximately 75 per cent of the patients. We have utilized this procedure in 9 patients and have been unable to duplicate the results obtained by others, since 4 of our patients have had proved recurrence of their disease and 3 others have had symptoms suggestive of recurrence.

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MAST CELL ACTIVITY UNDER VARIOUS FORMS OF STRESS

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Introduction and Previous Literature

THE mast cells of the connective tissue containing metachromatic granules have excited the interest of many investigators ever since their original description by Ehrlich.[18]

Ehrlich thought of them as being secretory cells but refused to speculate about what was being secreted. When Lison[23] began to stain connective tissue, it was found that the granules of the mast cell took on a purplish-red hue when stained with basic dyes such as thionin or toluidin blue. Why these granules contain heparin, histamine, and serotonin has been extensively discussed and documented in more recent literature.[5, 22, 27, 28]

The relationship of these important substances to each other has been the subject of a recent symposium on histamine.[9] It is interesting that heparin and histamine released from the mast cells do not seem to parallel each other but this may well be due to the heparin-inhibiting properties of some of the histamine releasers. Conversely, heparin has a partially inhibitory effect upon the release of histamine from cells to plasma.[17] As far as serotonin is concerned, it is widely distributed in platelets, in the gastrointestinal tract, in the hypothalamus, and in the mast cells of the rat.[5] There is about one part serotonin to 24 parts of histamine, and this substance seems to contribute to the hyperemia and edema of inflammation.[5]

Our own interest in studying the behavior of mast cells under various forms of stress stems from 2 clinical observations. The first one had to do with increased sensitivity of patient to heparin when receiving sulfur compounds such as sodium thiosulfate, sodium tetrathionate, or sulfapyridine[11] (Figs. 1 and 2).

Clinically, inorganic sulfur compounds have been used by several investigators in the treatment of thrombophlebitis and the acute stages of thromboangiitis obliterans.[11] This observation takes on added significance since the findings of Asboe-Hansen[2] that radioactive sulfur (S^{35}) is taken up by the majority of mast cells. The mast cells are said to be intimately associated with sulfate metabolism just like all substances containing mucopolysaccharides are.

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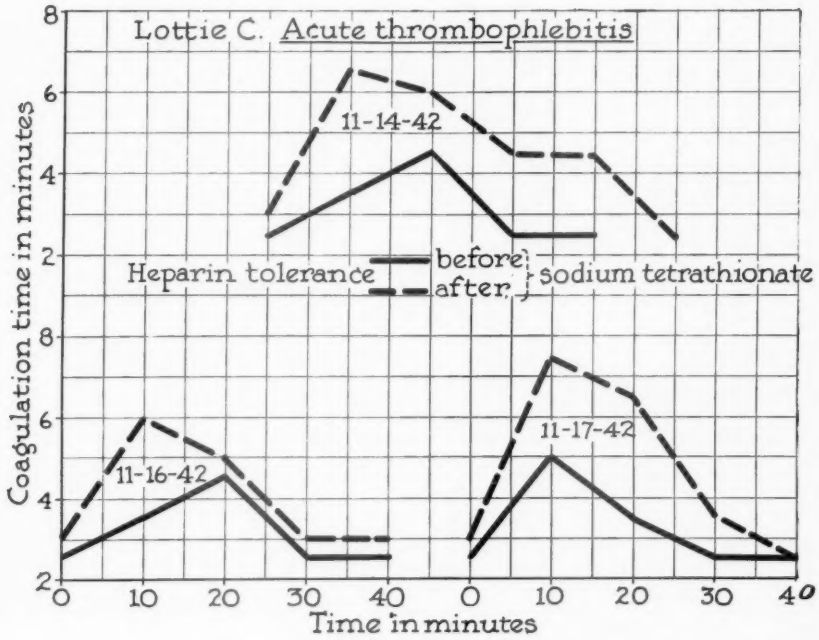

Fig. 1.—Heparin tolerance curves before and 10 minutes after the injection of 0.6 Gm. (10 gr.) of sodium tetrathionate. The tolerance curves on 11-14 and 11-16 are flat but become normal after the sulfur compound is administered. On 11-17, the tolerance curve is normal (at least double the preinjection level at 10 minutes) and is markedly exaggerated after sodium tetrathionate. Capillary coagulation times in minutes. 10 mg. of heparin intravenously at 0 minutes. (From de Takats, G.: SURGERY 14: 661, 1943.)

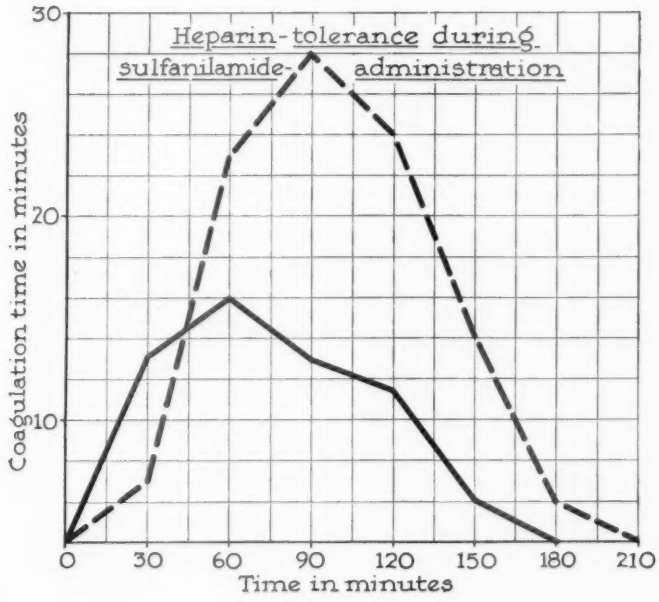

Fig. 2.—Straight line: capillary coagulation times after 50 mg. of heparin given intravenously. Interrupted line: tolerance curve after the same dose in a 26-year-old patient with rheumatic heart disease and subacute bacterial endocarditis receiving 120 grains of sulfapyridine daily. The sulfapyridine level was 4.2 mg. per 1,000 c.c. of blood on the day of the test. (From de Takats, G.: SURGERY 14: 661, 1943.)

The second observation reported by one of us with Voigt[13] concerned the fact that when ACTH was given intramuscularly in single or repeated doses, the drop of eosinophils was accompanied by a significant rise in sensitized clotting times in a normal individual (Fig. 3) but not in a patient with thromboembolic disease. In trying to study the probable mechanisms which would release anticoagulant substances after ACTH, we thought that possibly mast cell disruption might be one factor.

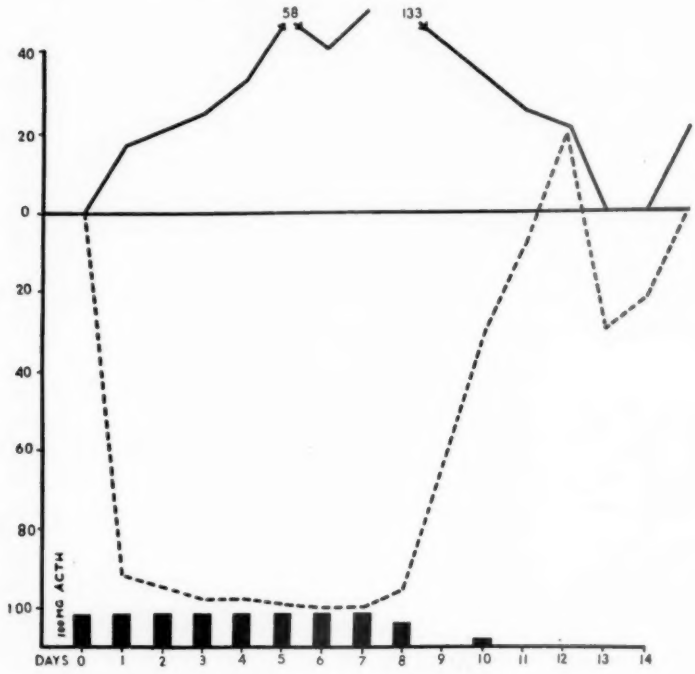

Fig. 3.—Percentage fall of eosinophils and rise in clotting times during daily injections of 100 mg. of ACTH (percentage change in clotting time ———; percentage change in eosinophils - - - - -). No thromboembolic disease was present. (From de Takats and Voigt, Angiology 4: 283, 1953.)

This study was undertaken for the purpose of: (1) studying the normal basic behavior of the mast cell, (2) observing the histologic effects of preloading the mast cells with heparin, (3) watching the effect of ACTH on the normal and on the previously heparinized mast cell, and (4) evaluating other agents which might possibly degranulate mast cells and release their content. Obviously, the staining method had to be carefully standardized since the vulnerability of mast cells to minimal stimuli including hypotonicity and change in pH are sufficiently known. Evidently the mast granule is an intracellular osmometer from which heparin can be released as hydration occurs.[28]

Opinion as to the effect of ACTH acting through cortisone on the mast cells is divided. Asboe-Hansen,[3] Stuart,[33] Cavallero and Braccini,[8] Bloom,[6] Fulton and Maynard[20] believe that this hormone decreases the number of and degranulates the mast cells. Negative findings were reported, however, by Schoch and Glick[30] and by Devitt, Pirozynski, and Samuels.[14] Hardly 2 investigators have used the same staining methods, and the conflicting results may be due, at least in part, to technique of fixation and staining.

METHODS OF STUDY

The recently published simple and rapid staining procedure of Smith and Atkinson[31] was modified. Normal albino rats weighing from 175 to 200 Gm. were anesthetized with intraperitoneal Nembutal. After a laparotomy, a glass slide was slipped into the abdominal cavity, then a freely movable intestinal loop was gently picked up, and the mesentery was spread on the slide with a minimum of trauma. With a clean, quick cut of sharp scissors, this segment was freed of its mesenteric attachment, fixed in absolute alcohol for 8 hours and stained by immersing the slides for 15 seconds in 0.5 per cent solution of toluidin blue. The slides were then gently rinsed for 1 to 2 seconds with 95 per cent alcohol, cleared through xylene for 12 hours, and mounted with Clarite under a glass overslip. Care was taken to strictly observe these time relationships and to never vary the concentration of the basic dye.

The mast cells of the rat mesentery were then observed under the following conditions: (1) In a group of 10 normal rats, 20 fields were counted of each mesentery, with care being taken to count 10 fields in the perivascular areas and 10 fields in avascular connective tissue. Since mast cells are encountered in various stages of development, maturity, and degranulation, the percentage of "abnormal" mast cells was noted. All cells showing karyorrhexis, karyolysis, vacuolization, and rupture of cellular membrane with a halo or scattering of granules were counted as abnormal. An N.A. 66 Spencer objective ×93 and a ×15 ocular lens was employed. This magnification was used in all the other counts. (2) In a group of 10 rats, 10 mg. of ACTH was injected intramuscularly and the mast cells observed 4 hours after the administration of the drug. (3) A third group of 10 rats was given 4 mg. of heparin intramuscularly for 5 days. On the fifth day, 10 mg. of intramuscular ACTH injection was given 4 hours after the last dose of heparin. Mast cells were observed 4 hours after the injection of ACTH. (5) Twenty animals in this group were given nitrogen mustard. They were divided into 4 groups, each containing 5 rats. Each subgroup contained 3 treated animals and 2 controls. Nitrogen mustard was given intravenously in doses of 0.5 mg. per kilogram of body weight. The controls received isotonic solution of sodium chloride of equal volume, that is, 1 c.c. The injections were given and the mast cells were studied 20 minutes later according to the following pattern: (a) *The first day* all animals received nitrogen mustard or saline. The first group of 5 animals were explored and their mesenteries studied for mast cells. (b) *The second day all* remaining animals received a second dose of nitrogen mustard and the controls received saline solution. A second group of 5 animals were anesthetized and their mast cells observed. (c) *The third day* a third dose of the drug was given to all the remaining rats, the controls receiving saline solution. Another group of 5 rat mesenteries were studied. (d) *The fourth day* the last group of rats were injected with nitrogen mustard or saline, respectively, and their mesenteries were observed. Thus, we had rats receiving 1, 2, 3, and 4 injections of nitrogen mustard on successive days with appropriate control injections of saline. (6) In a sixth group of 10 rats, a nonanaphylactogenic

polysaccharide, piromen (Baxter) was injected in a single dose of 0.5 micrograms. Mast cell counts were done at the height of the rectal temperature which proved to be at 3 hours. (7) A last group of 10 rats were given 700 roentgen units as a total body irradiation. They were observed 25 days after the administration of this dose.

RESULTS

1. In the group of normal controls, circular fusiform or oval cells were observed measuring from 5 to 30 micra in diameter. Their cytoplasm was homogeneously packed with metachromatic granules. Most of the cells exhibited a central nucleus. The cells were distributed mainly around blood vessels, often in rows parallel to them (Fig. 4). This perivascular arrangement was more frequent than their distribution in avascular areas (Fig. 5). The perivascular mast cells showed orthochromatic staining with some metachromatic granules, whereas the ones in the connective tissue showed overwhelmingly metachromasia (the purple-red color), an observation stressed previously by Riley and West.[29] The total number of cells counted was 36,745, 23 per cent of which were vacuolized, degranulated, or disrupted.

2. In the group of rats receiving ACTH, 30,020 cells were counted. Vacuolization, degranulation, and disruption were observed in 52.8 per cent of the cells, confirming the findings of Asboe-Hansen[3] and others (Fig. 6).

3. After 5 days of heparin administration, the mast cells stained much more deeply than in the normal controls, a fact more readily seen in Kodachrome slides, although a black and white print may indicate it (Fig. 7). There also seemed to be a numerical increase in metachromatic cells readily demonstrable under low power (Fig. 8). In this group, a total of 66,423 cells were counted with disruption amounting to 31.8 per cent.

4. In the group heparinized and then injected with ACTH, the absolute number was increased from the normal (59,427 cells) and the amount of abnormal cells was higher, 66.9 per cent. There seemed to be, however, a slight decrease of total cells when compared to those given heparin alone, roughly 7,000 cells less in 20 fields. A great number of metachromatic granules were scattered in the connective tissue; the granules were often visible at great distance from the parent cell and vacuolization was prominent (Fig. 9). Around some cells a purplish halo was visible consisting of nongranular material just like the phenomenon observed by Paff and Bloom[26] in vitro, indicating that metachromatic material has left the cell in solution.

5. In the group given nitrogen mustard, the highest amount of mast cell disruption was observed (Fig. 10). In the 4 groups receiving this drug on successive days, the cellular abnormality was 90.6, 86.1, 89, and 87 per cent, respectively. The absolute number of cells decreased from a control of around 5,000 cells to 3,527, 3,245, 2,894, and 2,647 cells, respectively. While the first injection of NH_2 produced the highest disruption of the mast cells (90.6 per cent), the greatest structural damage appeared in the last group, which had received 4 doses of nitrogen mustard.

Fig. 4.

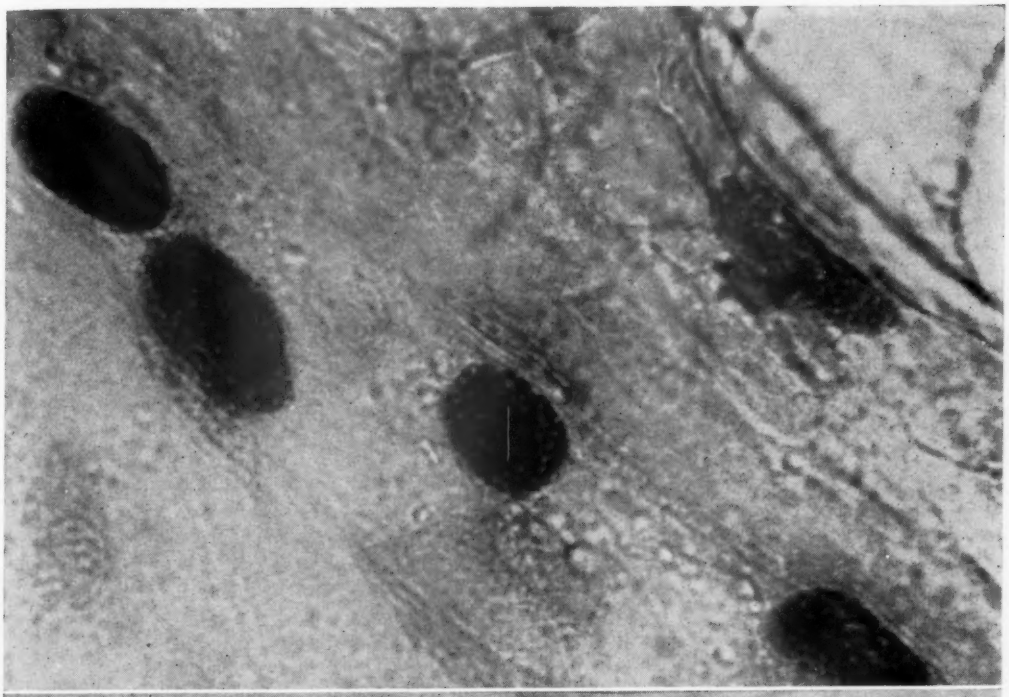

Fig. 5.

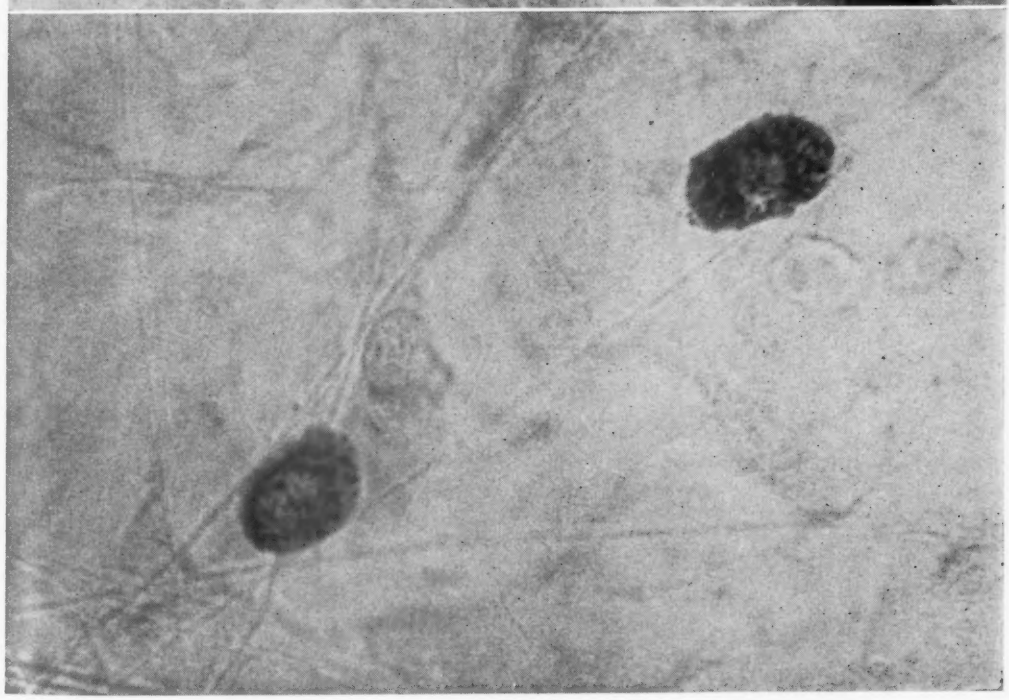

Fig. 4.—Perivascular mast cells showing large granules with orthochromatic staining in the Kodachrome slides. The elongated cell in the left upper quadrant shows some vacuolization and extrusion of granules. (×1,900, ¼ off reduction.)

Fig. 5.—Two mast cells in avascular connective tissue. The granules here have a purplish hue in the colored slide. The difference between these cells and the perivascular ones shown in Fig. 4 is probably that of maturity and increased secretory activity. (×1,900, ¼ off reduction.)

Fig. 6.

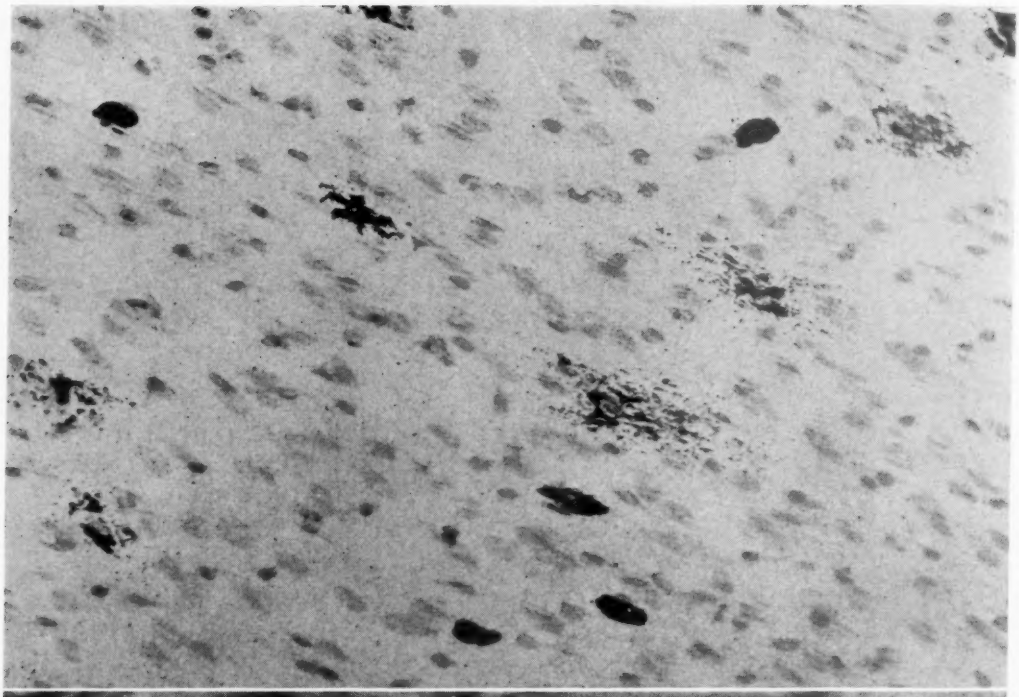

Fig. 7.

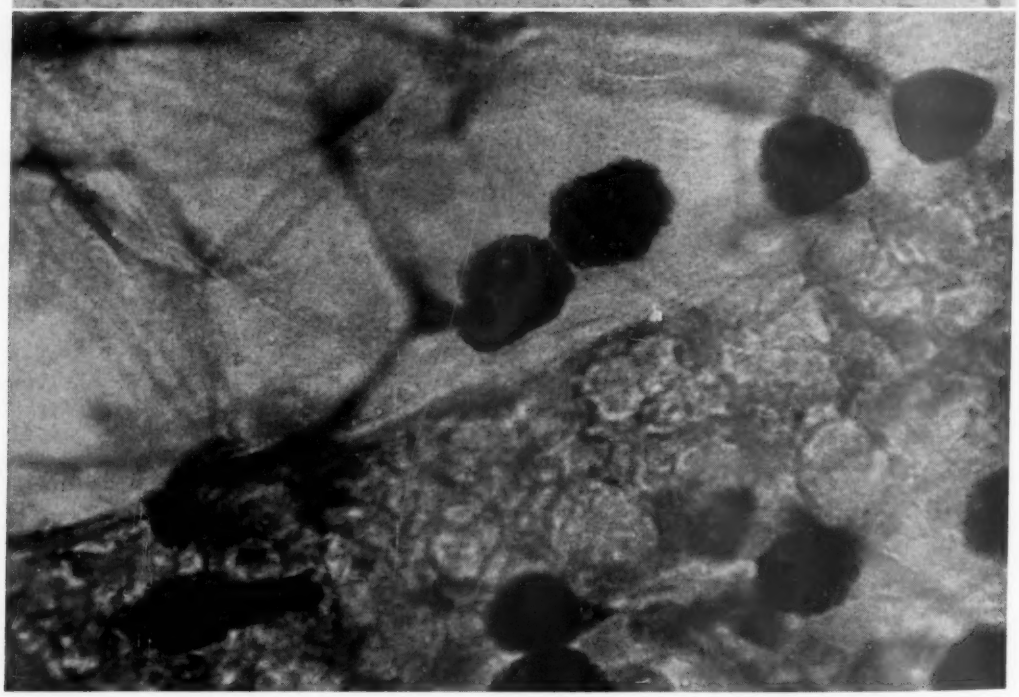

Fig. 6.—Effect of ACTH on mast cells. In this field, 7 of 11 mast cells are disrupted with metachromatic granules visible at considerable distance from the parent cell. (×500, ¼ off reduction.)

Fig. 7.—Heparinized mast cells in a perivascular area. They stain deeply and are loaded with granules. (×1,900, ¼ off reduction.)

Fig. 8.

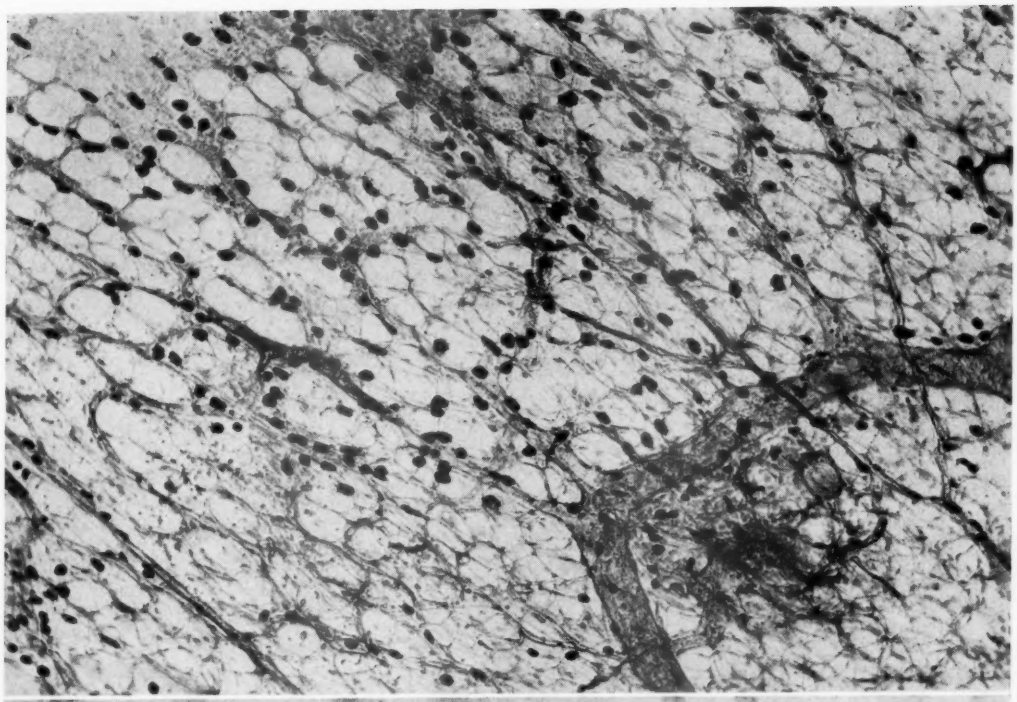

Fig. 9.

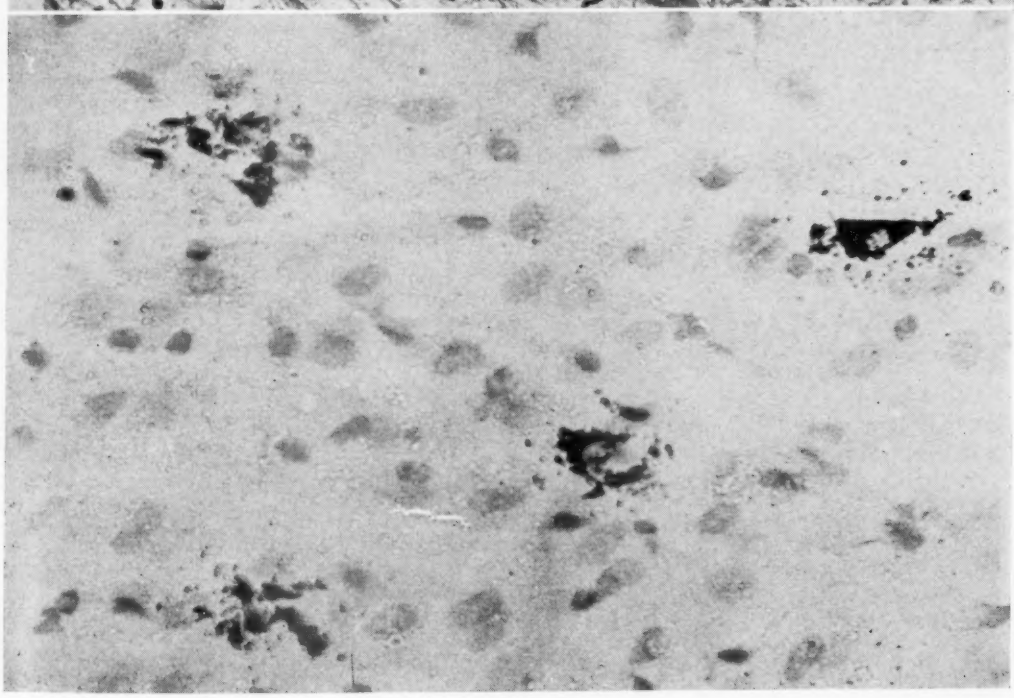

Fig. 8.—Rat mesentery after saturation of the animal with heparin. There seems to be little if any disruption of these cells and their number is obviously increased. (×320, ¼ off reduction.)

Fig. 9.—The effect of ACTH in heparinized rats. All 4 mast cells have ruptured, with granular material visible at considerable distance from the parent cell. The fate of these granules will be discussed under comments. (×1,900, ¼ off reduction.)

Fig. 10.

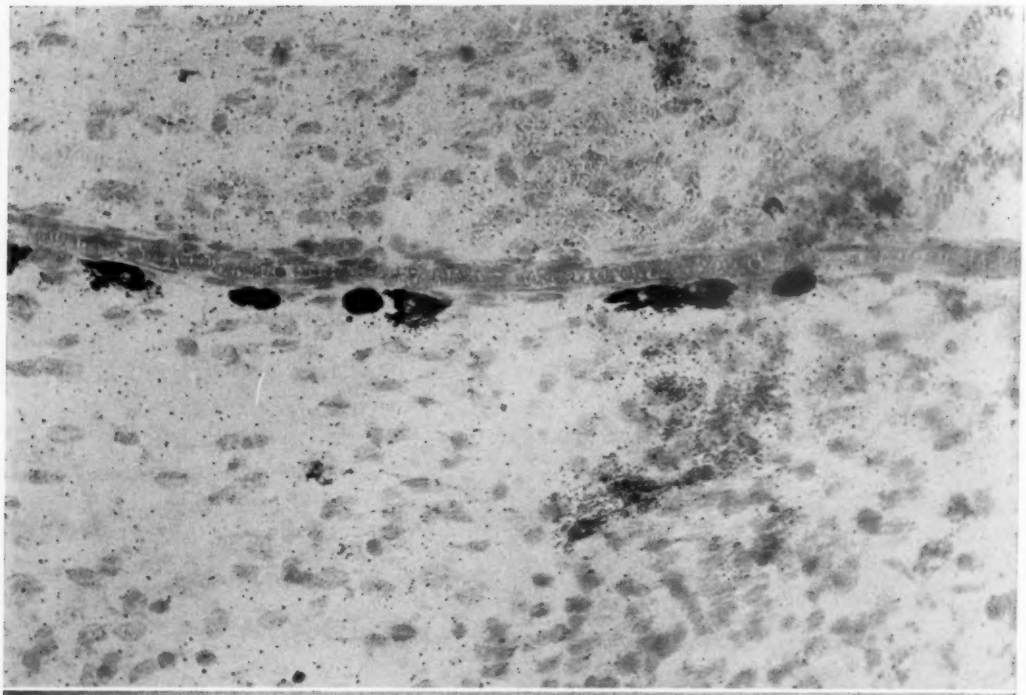

Fig. 11.

Fig. 10.—Widespread degranulation and scattering of metachromatic granules is seen after nitrogen mustard. The small vessel coursing through the center of the field does not seem to take up any of the granules. (×500, ¼ off reduction.)

Fig. 11.—The 5 mast cells seen in the field are all vacuolized after the injection of Piromen. The granules are faintly stained in the connective tissue. (×500, ¼ off reduction.)

6. After the intravenous injection of Piromen, the rat's rectal temperatures rose from 97.0° to 98.5° F. to a peak of 102°, 103°, and 103.5° F. at 3 hours. At this time, the mast cells were counted and observed. The total number counted in 20 fields was 32,597, and the disruption was 57.6 per cent. Mast cell disruption after Piromen has also been seen by Dougherty[16] and Stuart.[33] The majority of abnormal cells had burst and their metachromatic content was scattered through the perivascular and avascular areas. Vacuolization was prominent in Fig. 11.

7. Twenty-five days after total body irradiation with roentgen ray, the mast cells showed degeneration with development of vacuoles, extrusion of granules, and poor metachromatic staining. Cells numbering 32,407 were counted and these changes were observed in 54.6 per cent of the counted cells. It should be noted that according to Smith and Lewis[32] the cells are beginning to recover at this time.

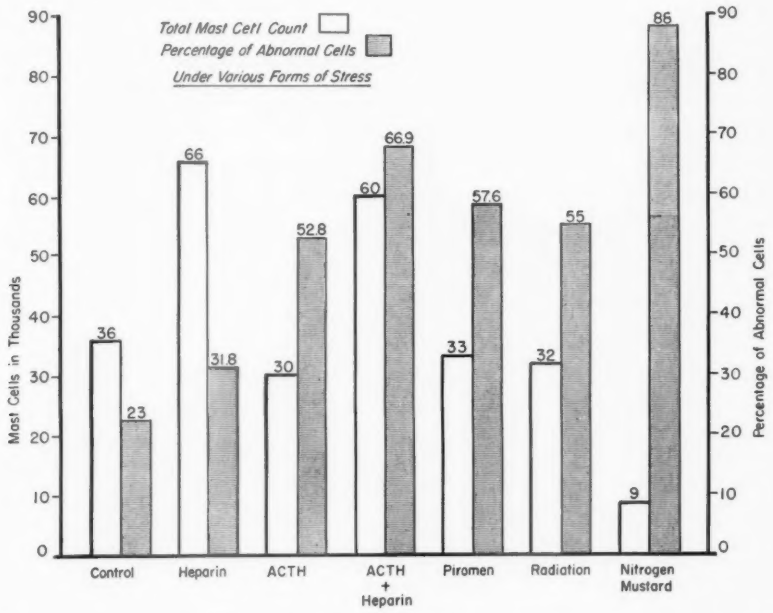

Fig. 12.—Normal mast cell counts are found in the rats treated with ACTH, Piromen, and radiation (30 to 36,000 cells in 20 fields). Heparin without or with ACTH doubles the number of mast cells (60 to 66,000). Nitrogen mustard cuts the count to about one fourth (9,000). The normal percentage of vacuolization, degranulation or disruption is 23 per cent. There is an increased percentage of abnormal cells with ACTH, radiation, Piromen, ACTH and heparin, and nitrogen mustard, in the order mentioned.

DISCUSSION

In summarizing the 7 groups of observations, the following statements may be made (Fig. 12).

In the normal albino rat, there is a continuous growth, maturity, aging, and disruption of mast cells so that a definite percentage of abnormal cells (23 per cent in this series) is always present. This fact so disturbed Devitt and Samuels[15] that they regarded all morphologic changes occurring after administration of various agents as being the result of artifacts. They properly

pointed out that fixation, dehydration, and staining techniques were all responsible for the abnormal characteristics. To this one might add that even the gentlest handling of the tissues might result in some mast cell injury and one can burst mast cells with distilled water hypotonic solutions and many histamine liberators.[15] We have however carefully kept all these factors constant and thus can show an increased percentage of vacuolization and disruption with ACTH, radiation, Piromen, and nitrogen mustard in the order mentioned. Since the total number of cells counted was considerable (290,857), we are dealing here with a direct action of the agents on mast cells even though the normal turnover of cells from formation to aging and death is well recognized and is true of all living cells.

The second point to be made is that the administration of heparin doubles the number of countable cells, that they stain more deeply, and that their disruption by ACTH is even more apparent. It was actually this point which we started out to investigate because of our clinical observations with heparin saturation before surgical stress.[13] On the basis of these findings we are inclined to believe that some of the heparin retained in the body is deposited or possibly resynthetized in the mast cell. A recent study of the fate of sulfur compounds tagged with S^{35} would suggest that even inorganic sulfur compounds may result in synthesis of heparin in the mast cells.[19] One is thus encouraged to continue the clinical practice of saturating the patient with heparin before certain operations or even using sodium thiosulfate for this purpose.[11]

We also wish to re-emphasize that the normal response of the clotting mechanism to postoperative stress is a lengthening of the clotting time[12] and one possible explanation may be the mobilization of anticoagulant substances from the mast cells. Thrombosis would then occur when this defense mechanism is exhausted. Of course, we are aware of other mechanisms, notably fibrinolysins, which have been under study for some time in this laboratory.

Piromen was used in this study for 2 reasons. First of all, many of the effects are mediated through the pituitary-adrenocortical axis and this is an indirect method of mobilizing ACTH. But also, foreign proteins were long in use in the treatment of thromboangiitis obliterans and one wonders whether in addition to the vasodilating effect some mast cell disruption might not be at play. We are not aware that protamine titrations have ever been done following the administration of Piromen.

Radiation, of course, destroys many cells and among the side effects of roentgen ray and also of nitrogen mustard is bleeding. Bleeding is usually explained by the low platelet counts but occasionally the protamine titrations do show an increase in anticoagulant substances.[1] Recent unpublished observations from this institution would indicate little if any increase in heparin-like substances after nitrogen mustard.[24] It has been shown, however, that protamine titration not only measures heparin but a host of other substances, notably mucoproteins, and only 1 per cent of the anticoagulant activity is due to heparin.[25]

One naturally wonders about the fate of the extruded metachromatic granules. S^{35}-labeled mast cell granules were made to erupt by mild trauma to the skin and were taken up by fibroblasts. This is a form of local detoxification[21] and may affect serotonin, histamine, and heparin alike.

The limitations of a histologic approach to the functional activity of a set of cells or an organ are obvious. Yet we forget that such studies may give an insight into the behavior of mast cells. So little is known about the significance of these cells around malignant tumors[7, 10] or in nutritional deficiencies[4] that a multifaceted approach, including histologic, isotope, and in vitro culture studies are rewarding.

SUMMARY

With the help of a simple, easily standardized staining method, the behavior of mast cells was studied on the rat's mesentery. In normal controls, it was possible to observe maturity, aging, and death of cells, although obviously the act of fixation and staining may cause artifacts. ACTH, radiation, Piromen, and nitrogen mustard caused much more than the normal amount of vacuolization and disruption of the mast cells. Heparin definitely deepened the staining quality of these cells and increased their number. ACTH readily emptied the granules of the heparinized mast cells.

These findings indicate that mast cell activity can be activated or increased by external stimuli. Loading of mast cells with heparin may make them available in times of stress. Thus a type of prophylactic preoperative anticoagulant therapy may find a sound basis.

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DIRECT VISION CORRECTION OF MITRAL INSUFFICIENCY

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MANY ingenious blind techniques have been devised and enthusiastically advocated in the recent past for the surgical correction of mitral regurgitation.[1-5] Invariably success was transitory and such operations were short-lived. The surgeons in this field have been aware in most instances of the inadequacies of such techniques and have continuously sought to devise improvements.

It has been apparent during this developmental phase of mitral valve surgery that further progress would come only when the mitral valve could be adequately visualized and the various pathologic factors appraised, evaluated, and corrected under direct vision, just as have the closed techniques for the correction of other cardiac defects given way to direct vision correction employing a mechanical pump-oxygenator. This phase necessitated the successful adaptation of extracorporeal circulation to left heart lesions. Experience gained from the use of the extracorporeal perfusion techniques in the correction of congenital right-sided lesions was beneficial. Additional factors, however, were present such as the proper exposure, the advisability or necessity of elective cardiac arrest, the prevention of air embolism, and the proper surgical techniques. Observations will be presented from both the research laboratory and the experience gained from the direct vision correction of mitral valvular disease in 17 patients. Thirteen patients were operated upon for mitral regurgitation and 4 for mitral stenosis.

PATHOLOGY

To surgically correct mitral insufficiency, the surgeon must have a knowledge not only of the structural changes present, but also of the relationship between structural changes and functional changes. Furthermore, functional changes in the case of valvular disease means motion—the proper opening and closing of the valve. Nothing short of observing the valve mechanism in the beating heart will allow the surgeon information as to the pathologic physiology of that patient's heart. Pathologically, there are two main types of mitral regurgitation—the pure and the mixed. In pure mitral regurgitation (Fig. 1, *A*), the valvular pathologic changes are at a minimum. Insufficiency of the valve is primarily the result of the dilated mitral annulus at the posteromedial commissure due to ventricular hypertrophy and dilatation in its attempt to compensate for the reduced cardiac output. The widening of the commissure and the separation of the cusps at this site undoubtedly result from the directional flow of blood through the aortic outflow tract. The factor of myocardial

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insufficiency assumes greater importance as the condition becomes worse. In this type, there is a relative loss of valve substance due to the increased size of the valve aperture.

The mixed type is composed of varying degrees of stenosis as well as regurgitation. The other lesions of rheumatic fever are also evident. There is an absolute loss of valve substance as a result of the cicatricial contraction of the valve leaflets. There are varying degrees of commissure obliteration giving rise to stenosis. The diseased chordae tendinae are fibrotic and foreshortened, which in conjunction with the inversion of the leaflets into the ventricular chamber and adherence to the endocardium causes the valve to have varying degrees of fixation in the open position. Again, in an attempt to compensate for the regurgitant flow of blood, the ventricle undergoes hypertrophy and dilatation, with consequent annular dilatation and aggravation of the pathologic process.

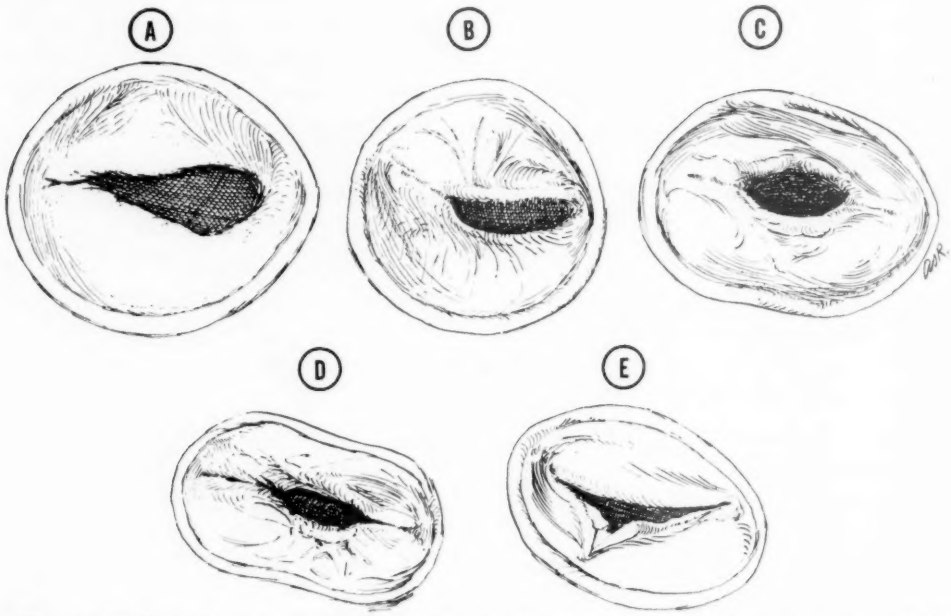

Fig. 1.—Pathologic configuration of mitral valve in patients with mitral regurgitation. *A*, Pure mitral regurgitation primarily due to relative loss of valve substance from annular dilatation. *B*, Mixed type of regurgitation with "teardrop" deformity resulting from obliteration of anterior commissure and dilated annulus at posterior commissure. *C*, Mixed type with "patulous" deformity resulting from obliteration of both commissures and central valvular contraction. *D*, Mixed type with "fish-mouth" deformity. *E*, Traumatic from previously attempted commissurotomy.

The mixed type may be predominantly regurgitant (Fig. 1, *B*), a combination of stenosis and regurgitation (Fig. 1, *C*), or predominantly stenosis (Fig. 1, *D*). As a result the configuration of the valve noted in the first would be "teardrop"-shaped, "patulous" in the second, and "fish-mouth" in the third.

In Fig. 1, *B*, the regurgitation is primarily at the posteromedial aspect of the valve. Varying degrees of obliteration of the commissures are also present; the greatest degree is at the anterolateral commissure. In Fig. 1, *C*, the contour of the orifice is round or oval. Both commissures are obliterated. The cicatricial contraction of the valve leaflets in their center gives rise to a patulous opening, which may be retracted toward the ventricle. In Fig. 1, *D*, which is primarily

stenosis, the degree of regurgitation through the residual opening that can be visualized with the auricle open has been considerably greater than what was detected with the palpating finger. One patient had a traumatic regurgitation secondary to a previous commissurotomy (elsewhere) in which apparently the commissurotomy knife severed the posterior leaflet (Fig. 1, *E*).

EXPOSURE

The mitral valve can be adequately exposed from either the left or right side. A left-sided exposure was used in 4 instances and a right-sided exposure in 13. The 4 patients in whom a left-sided exposure was used had only a small area of left auricle presenting on the right side. It was felt initially that this might limit the length of the incision in the auricle and in turn impair visibility if the mitral valve were to be exposed from the right side in such instances. Subsequently, it has been found that an adequate exposure can be obtained from the right side in spite of the amount of left auricular wall presenting into the right hemithorax. In the 13 patients in whom a right-sided approach was used, a considerable portion of the left auricular wall presented into the right thoracic cavity in 7 and only a minimal-to-moderate amount in 6.

It is felt that the right-sided approach is easier, better, and faster. It also does not entail as large a thoracotomy incision and is associated with less blood loss and operative trauma. It was also felt that the right-sided exposure could be obtained without stopping the heart and without the danger of air embolism. There was considerable support for this opinion from experience in the laboratory as well as from clinical observation. In no instance, either in animal experimentation or during open technique correction of patients with atrial septal defects, atrioventricularis communis, or transposition of the great vessels, has there been any evidence of air embolism. These patients were positioned in a similar manner with the right side of the body elevated approximately 20 degrees and the opening in the auricle being higher than the mitral valve.

AIR EMBOLISM

Experience gained in the laboratory showed that 50 per cent of the dogs had evidence of air embolism when the heart was not stopped with the mitral valve exposed from the left side. In this exposure the left atrium is more dependent than the aortic outflow tract and air tends to collect in this region. It was felt that the pumping action of the ventricle was pushing air into the circulation. Consequently, in later experiments, elective cardiac arrest was employed with reduction in the incidence of air embolism. In retrospect, one questions the validity of the initial impression, for the efficiency of the pumping action of the left ventricle in the open technique with the mitral valve open is probably not great enough to push air or foam through the aortic valve, which is firmly closed by the arterial pressure. It is important to maintain the mitral valve in a partially opened position to prevent the ventricular contraction from becoming effective so that air or foam cannot be pumped into the systemic circulation. The air probably had become entrapped in the higher located ventricular outflow tract and was not properly aspirated. The reduced

incidence of air following elective cardiac arrest experimentally was also associated with greater precaution in venting and flushing the left ventricular and auricular cavities of the residual air content prior to restarting the heart, and this latter factor is undoubtedly the reason for the lessened incidence of air embolism. In any event, as a result of this experience in the laboratory, cardiac arrest was employed in the 4 patients approached from the left side. One of these patients had evidence of air embolism. Transitory numbness and weakness of the left arm and leg persisted for 2 weeks postoperatively.

ADVISABILITY OF CARDIAC ARREST

Feeling initially that there was greater safety with the use of cardiac arrest, this was also utilized in the first 3 patients operated upon with the right-sided approach. Prior to closure the blood was allowed to accumulate in the left auricular chamber. No other measures were employed to prevent air embolism.

An attempt was made in the fourth patient approached from the right side to allow the heart to beat during the open cardiotomy. An undetected co-existent aortic regurgitation of not too great clinical significance allowed sufficient regurgitation of blood into the ventricular chamber to obscure visualization. Consequently, in instances of associated aortic insufficiency, cross-clamping of the aorta, with or without cardiac arrest, will be necessary. In bivalvular disease, particularly in the presence of aortic regurgitation, correction of the aortic valve should precede correction of the mitral valve.

The fifth patient, a woman aged 51, with considerable aortic and large vessel sclerosis, had a large friable clot within the auricle. The stenotic regurgitant mitral valve contained considerable calcium. It was thought advisable while removing the clot, which easily fragmented, to cross-clamp the aorta to minimize the likelihood of embolism. The heart was not stopped. Twenty-four hours after surgery there was evidence of facial nerve weakness which persisted for about 10 days. This was thought to be embolic from the clot or calcium, rather than air embolism.

The remaining 8 patients have had their surgical correction of the mitral insufficiency with the heart beating, without evidence of embolic phenomena. The left auricle is first explored with the intracardiac finger. It is then widely opened to determine the characteristics of the regurgitation. When tension is placed on the valve, particularly on the anterior or aortic cusp of the mitral valve to enable surgical maneuvers, the aortic annulus may be distorted and considerable aortic regurgitation may ensue with obscuration of the operative field. At this time the aorta may be temporarily clamped to insure a dry field without impairment of visualization to allow for the commissurotomy and to set the first suture for the annular plication. The aortic clamp is then released, allowing flushing of the ventricular chamber of any air. Additional annular plication as needed is then performed, with the heart beating to assure functional closure of the valve during ventricular systole.

There are other advantages in allowing the heart to beat. To begin with, more information can be obtained from the visual observation of the factors contributing to the regurgitation with the heart beating than can be obtained by

digital exploration prior to elective cardiac standstill. The location of the regurgitation, although predominantly at the posteromedial commissure, is not always constant.

Furthermore, it should be obvious that it is impossible to verify whether complete correction of the regurgitation has been obtained unless it is tested with the heart beating. The 2 patients who obtained either a fair or poor result had their correction accomplished during elective cardiac arrest. The steps necessary to accomplish correction, although directed toward valve mobilization and approximation by decreasing the size of the mitral annulus, vary with the individual patient. It is impossible to obtain this desired result without observing what is being accomplished. This can be exemplified in the case of a patient with a highly calcified valve of the "teardrop" type of deformity. Correction of the regurgitation at the posteromedial commissure by approximation of the anterior and posterior limbs of the annulus at this site allowed the valve cusps to coapt and stopped the regurgitant jet of blood. However, there was distortion of the rigid valve which allowed regurgitation at the anterolateral commissure, which necessitated correction at this site as well.

Other advantages of allowing the heart to beat are that such operations need not be hurried. The impaired myocardium is kept well oxygenated and there is no danger of difficulty in restarting the heart which may be encountered in patients when the myocardial reserve is poor and which may be further harmed by the detrimental effects of potassium and anoxia. There has been no apparent harm resulting from the use of temporary or intermittent aortic occlusion if employed during the procedure to allow a drier field during the initial placement of the sutures.

TECHNIQUE

A right anterolateral incision through the fourth intercostal space is made with transection of the sternum, if necessary. The patient is positioned with approximately 20 degrees of elevation of the right side. Manometric pressure recordings in the base of the aorta, left ventricle, and left auricle are taken, evaluated, and correlated with the preoperative cardiac evaluation studies before the cannulations are made. The various anatomic, pathologic, and physiologic aspects of the mitral valve are then determined by digital examination prior to opening the auricle in an attempt to assess the various contributing factors and to formulate the plan of attack. In patients with the mixed type of mitral insufficiency, as much of the commissurotomy and valve leaflet mobilization as is possible is performed by closed digital manipulation before the auricle is widely opened. Total cardiopulmonary bypass by means of the pump-oxygenator is then instituted to allow further correction of these aspects under direct vision. After the maximum valve orifice and valve mobility is obtained by commissurotomy, the site and degree of regurgitation are again appraised. If the regurgitation is primarily at the posteromedial commissure, the valve cusps are approximated by plicating the annulus with linear sutures placed in the anterior and posterior limbs of the mitral annulus above and below the posteromedial commissure as demonstrated in Fig. 2, *B*.

In some instances, particularly with the patulous type (Fig. 1, *C*), when there is a general regurgitation of blood throughout the orifice, both commissures are first widely opened, following which it is necessary to plicate the annulus at both commissures in order to accomplish cusp coaptation (Fig. 2, *C*). Occasionally it has appeared beneficial to include a plug of Ivalon sponge to fill the reduced space between the limbs of the annulus at the site of plication when complete approximation has produced an overlapping of the cusps or an undesirable amount of restriction of the orifice (Fig. 2, *D*).

In some instances, and this is more likely to be true of patients with pure mitral regurgitation with a markedly enlarged annulus, it is desirable to reduce the size of the annulus by linear plication at multiple points around its circumference as noted in Fig. 2, *A*.

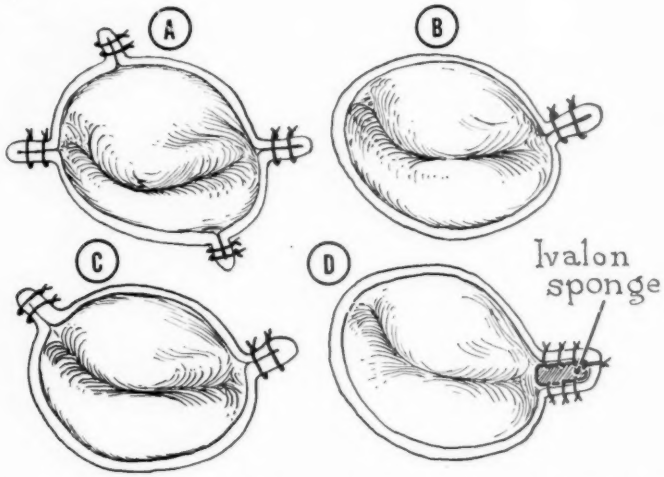

Fig. 2.—Diagrammatic sketches of variety of annular plication used in correction of mitral regurgitation. *A*, Multiple point plication used primarily in patients with pure mitral regurgitation. *B*, Medial annular plication used primarily in patients with "teardrop" deformity. *C*, Bilateral annular plication used primarily in patients with "patulous" deformity. *D*, Utilization of Ivalon plug to prevent overlapping of valve cusps.

Blood is allowed to accumulate in the auricle prior to closing. It the patients in whom elective cardiac arrest was employed, transventricular or transaortic aspiration of the base of the aorta and ventricular outflow tract for entrapped air was performed while releasing the aortic clamp. Temporary carotid occlusion by the anesthetist perhaps also aided in avoiding cerebral air embolism. Four of the 8 hearts in which elective cardiac arrest was employed had ventricular fibrillation treated by electric shock. The duration of the cardiac arrest varied between 15 and 35 minutes. There was spontaneous resumption of the normal heartbeat in the other patients. There have been no arrhythmias in the 9 patients in whom intermittent aortic occlusion was employed, even though the occlusion existed as long as 4 to 5 minutes in some instances.

The patients ranged from 19 to 51 years of age and weighed between 108 and 187 pounds. A rotating disk-type oxygenator was employed in all patients with flow rates ranging from 60 to 80 c.c. per kilogram per minute. During the

perfusion there was constant monitoring of the mean arterial and vena caval pressure, constant blood balance, electroencephalogram, electrocardiogram, oxygen saturation, oxygen tension, and carbon dioxide tension. There was intermittent monitoring of blood buffer base, pH, hemoglobin, and hematocrit. Pressure recordings were taken again prior to closing for comparison with the preoperative determination. The recordings in the last 4 patients since this policy has been instituted are demonstrated in Table I.

TABLE I. PRESSURE RECORDING LEFT AURICLE (MM. HG)

PATIENT	PREOPERATIVE	POSTOPERATIVE
J. W.	30/25	18/4
V. B.	68/46	12/4
M. L.	42/19	22/15
F. B.	70/22	36/16

RESULTS

There was one operative death in this series. This was the first patient to be operated upon. This patient had been operated upon previously. The lungs were congested and other evidence of cardiac failure was present, including pleural fluid, an enlarged liver, and peripheral edema. A left-sided approach was employed. The operation was long and bloody. A blood imbalance was present at the end of the procedure which, in combination with a prolonged cardiac arrest of 35 minutes and myocardial insufficiency, contributed to this failure. There was one other patient not included in this series who had been in severe failure for 2 years. This patient had a failing and enlarging heart on strict medical regimen. He had both aortic and mitral insufficiency. Ventricular fibrillation and cardiac standstill occurred even before the cannulations were performed, which required some time before re-establishment of the normal beat. The aortic regurgitation was first corrected by the direct vision technique using elective cardiac arrest. The heart was then restarted for 10 minutes followed by a second period of cardiac arrest to correct the mitral regurgitation. Four fingers could easily be inserted through the mitral valve. The heartbeat was then again re-established, but the patient died approximately 2 hours later. Two of the patients operated upon through the left-sided approach employing cardiac arrest have had, in one instance, a poor result and, the other, only a fair result. In retrospect it is felt with the heart stopped it was impossible to evaluate properly the residual insufficiency and to take the necessary steps to correct it. The others have all done well for periods of 2 to 8 months. The long-range evaluation, of course, is impossible at this time.

COMMENT

It is felt that with the use of a mechanical pump-oxygenator, direct vision correction of mitral regurgitation will now be a realization. It has been demonstrated that even with the initial series of far-advanced patients, the operative mortality and morbidity are extremely low. Definite factors in this mortality and morbidity are the myocardial insufficiency and pulmonary vascular disease

present in the far-advanced patient. Now that we have a safe and assured method of treating such patients, operative intervention should be employed before irreparable damage occurs.

SUMMARY

At present thirteen patients with mitral insufficiency and 4 patients with mitral stenosis have been operated upon employing a rotating disk-type oxygenator and direct vision correction of the valvular defect. Various aspects of the surgical approach with and without cardiac standstill have been employed and discussed. It is felt that the right-sided approach to the mitral valve allowing the heart to beat during the surgical correction, but with intermittent aortic occlusion, will be associated with the greatest number of successful results. The surgeon must, however, be able to vary his operative technique to best cope with the individual problems presented in each patient.

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THE ELECTRONIC MEASUREMENT OF CARDIAC OUTPUT

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CARDIAC output determinations are extremely valuable in a variety of clinical and experimental conditions. Often, knowledge of the cardiac output figure has value in itself. This determination becomes almost indispensable in evaluation of a variety of hemodynamic alterations resulting from surgical procedures or administration of pharmacologic agents. Changes in pressure or flow in a given vessel or organ in response to some experimental procedure must be evaluated against the background of the simultaneous alteration in cardiac output which might result from the experimental procedure.

A variety of methods for determination of cardiac output have been described and of these the direct Fick and the dye dilution enjoy well-deserved current popularity. The direct Fick method is completely sound in principle but has several practical defects in application. It is difficult to get a "mixed" venous sample in which the investigator has complete confidence. This is the greatest variable in the method; total oxygen consumption and arterial oxygen content usually remain relatively constant over a study interval. The second defect is that a minimum of several minutes is required to obtain an oxygen consumption rate; therefore, rapid alterations cannot be observed but rather only those in comparatively steady states. Finally, the results of the determination are usually not available to the investigator until after the procedure is completed, usually several hours later, due to the time required in making blood gas analyses.

Although the dye dilution technique has undoubtedly produced much valuable information,[4] there still remains some doubt as to its theoretical validity and there are very real practical problems in collection of samples.

This paper describes a new electronic technique for measurement of cardiac output which has some advantages over the methods just mentioned as well as certain limitations.

METHOD

Under minimal intravenous barbiturate anesthesia and intermittent positive pressure respiration, the left thorax was entered in a series of 10 dogs. Following the minimum dissection required for exposure, flow measurements were made in the brachiocephalic artery, left subclavian artery, and descending aorta just beyond the origin of the left subclavian. The flow measurements were made using the electromagnetic flowmeter as described by Denison,

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Spencer, and Green.[3] This instrument enables accurate measurement of flow through exposed but unopened blood vessels. The points at which flow measurements were made are illustrated schematically in Fig. 1, as points *A*, *B*, and *C*. A flowmeter probe is illustrated in place on the left subclavian artery.

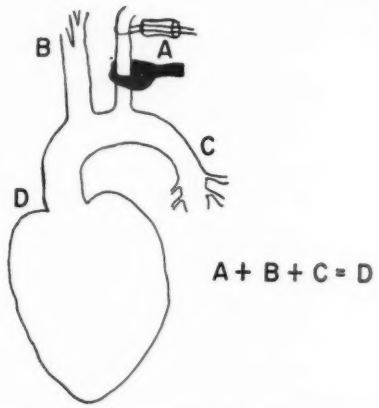

Fig. 1.—Site of flow measurements.

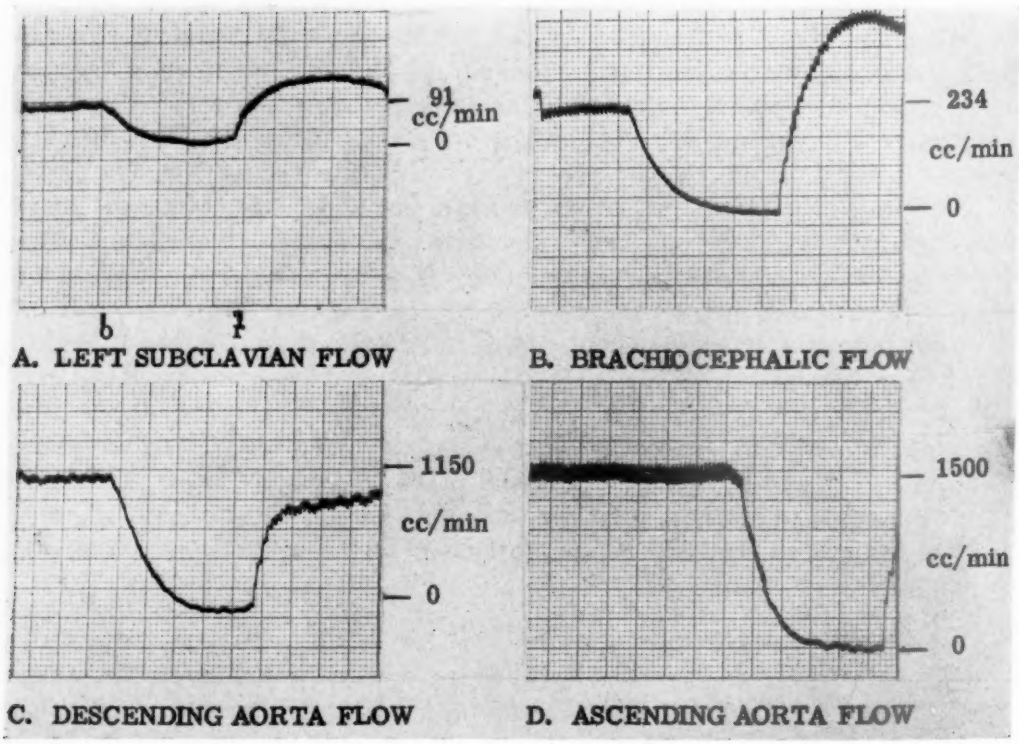

Fig. 2.—Electromagnetic determination of cardiac output.

In 3 animals the ascending aorta was dissected free and flow measurements made at point *D* as well as the others just described. This method requires momentary occlusion of the vessel downstream from the flowmeter probe for establishment of the zero flow base line and the tape used for this purpose is shown distal to the probe at point *B*.

TABLE I. ELECTROMAGNETIC MEASUREMENT OF CARDIAC OUTPUT

DOG NUMBER	WEIGHT (KG.)	A	B	C		D
		SUBCLAVIAN (C.C./MIN.)	BRACHIOCEPHALIC (C.C./MIN.)	DESCENDING AORTA (C.C./MIN.)	LEFT VENTRICULAR OUTPUT* (C.C./MIN.)	LEFT VENTRICULAR OUTPUT* (C.C./KG./MIN.)	ASCENDING AORTA OUTPUT (C.C./MIN.)
3	14.5	154	286	1,250	1,690	117	—
6	31.0	460	530	2,200	3,190	103	—
16	20.0	221	520	1,200	1,941	97	—
34	16.8	264	380	1,320	1,964	117	—
38	22.7	253	450	1,440	2,143	95	—
48	25.0	220	435	2,640	3,295	131	—
31	14.1	253	644	864	1,761	125	1,824
39	23.5	364	546	2 200	3,110	136	3,200
5	14.1	91	234	1,150	1,475	105	1,500
52	15.0	—	—	—	—	147	2,200
					Average	117	—

*Less coronary flow.

RESULTS

Actual flow patterns from one experiment are shown in Fig. 2. Each curve shows a steady flow value just prior to occlusion and a precipitous fall to the zero reference point on occlusion followed by resumption of flow after release, often with momentary overshoot of flow. The calibration depends upon the probe used to fit a given vessel; hence it varies in the curves shown. The appropriate calibration is indicated on each curve. The total time required to make each flow determination was less than 27 seconds; the latter figure is the timed total length of recording for each of the tracings shown.

The results for the series of animals are shown in Table I. The left ventricular output (less coronary flow) varied from 95 to 147 c.c. per kilogram per minute with a mean value of 117 c.c. per kilogram per minute.

The results of the measurement of ascending aorta flow as compared with the 3 distal segments are shown in Table II. The maximum difference by the 2 methods of measurement is 3.6 per cent and is negligible since the accuracy of the flow determinations in our hands is only ± 5 per cent for these large flow determinations.

TABLE II. ASCENDING AORTA FLOW DETERMINATIONS AS MEASUREMENT OF CARDIAC OUTPUT

DOG NUMBER	POINT AT WHICH FLOW MEASURED	FLOW (C.C./MIN.)
5	D	1,500
	A + B + C	1,475
39	D	3,200
	A + B + C	3,100
31	D	1,824
	A + B + C	1,761

DISCUSSION

There are advantages in this method of determination of left ventricular output which are immediately apparent. Foremost among these is the fact that the left ventricular output can be determined almost instantaneously and the value read directly from a recorder. An output determination can be made in 20 seconds. Furthermore, continuous observation and recording of left ventricular output over a long period of time is simple using this technique. The most obvious objections to this method are the fact that it must be carried out under general anesthesia, using positive pressure respiration, and through the open thorax. While these conditions prevent application of this method under basal conditions, the method retains all of its value under experimental or operative conditions where anesthesia and the open chest are already required in order to carry out the surgical procedure or experimental manipulation desired.

This method completely neglects coronary flow which is thought to represent 5 per cent or less of the left ventricular output.[2] It is doubtful whether any one of the methods for determination of cardiac output is accurate enough to reflect changes in coronary flow.

The cardiac output figures reported above cannot be compared with figures obtained under basal conditions, but Berne and Levy[1] report cardiac

output under conditions very similar to ours. They determined the cardiac output by the direct Fick method in dogs under barbiturate anesthesia with the left chest open and after dissection at the base of the aorta and pulmonary artery. Comparison of their cardiac output figures from 8 experiments with ours from 10 experiments is made in Table III. The correlation of the 2 mean figures is very close but both experimental groups are small.

TABLE III. CARDIAC OUTPUT UNDER BARBITURATE ANESTHESIA WITH OPEN THORAX

	RANGE OF CARDIAC OUTPUT (C.C./KG./MIN.)	MEAN CARDIAC OUTPUT (C.C./KG./MIN.)
Present study	95-147	117
Berne and Levy[1]	69-179	116

The electromagnetic method for determination of cardiac output has another real advantage in that the same method can be applied to a variety of peripheral and visceral vessels as well as estimating cardiac output. The estimation of cerebral, renal, visceral, and somatic blood flow and cardiac output all by different methods resulted in the dilemma of the total of the individual flow estimations exceeding the cardiac output.[5] The same electromagnetic technique can be applied to any vessel which can be surgically exposed; thus errors inherent in methodology will remain relatively constant and comparative values become more meaningful. McMichael states: "We are still lacking a method of proven value to give us the rate of change of cardiac output from beat to beat."[6] It might be anticipated that the method here presented, or some modification of it, might fulfill this need.

SUMMARY AND CONCLUSIONS

1. A method is described for measurement of cardiac output utilizing the electromagnetic flowmeter.

2. Cardiac output may be measured either by recording flow from the ascending aorta alone or from the sum of the flows from the descending aorta and aortic arch branches.

3. This method neglects coronary flow.

4. Cardiac output determination in 10 dogs under intravenous barbiturate anesthesia with the left chest opened showed a mean value of 117 cc. per kilogram per minute with a range of 95 to 147 c.c. per kilogram per minute.

5. Instantaneous and continuous recording of cardiac output may be obtained by this method.

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VENOUS PATTERNS FOLLOWING OCCLUSION OF THE JUGULAR SYSTEM AS DEMONSTRATED BY JUGULAR VENOGRAPHY

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IN THE performance of radical dissection of the neck for tumors involving the structures within the oral cavity, pharynx, larynx, or thyroid gland, major venous channels, especially the jugular system, unilaterally or bilaterally are frequently excised. The resultant signs indicative of impaired venous drainage from the head are obvious in some, mild or transitory in others. It has been presumed after surgery of this character that residual venous channels, such as the vertebral, opposite internal jugular if present and patent, and possibly the pharyngeal plexuses, assume the burden of venous drainage of the head. However, specific data regarding such ancillary avenues for venous flow are sparse. Dixon[1] in 1934, using primarily animals, demonstrated by roentgen technique the cephalic venous circulation following injection of a radiopaque substance into a lingual vein. Freuchner[3] injected contrast medium in the superior sagittal sinus through a small drill hole in the posterior parietal area. Ellis[2] and Scott[6] both visualized the superior sagittal sinus radiographically in children by means of instillation of contrast medium through an open anterior fontanel. Guis and Grier[4] used a vein over the forehead for the avenue of injection of a contrast substance. Ray[5] utilized 2 methods for visualization of the venous drainage of the structures of the head: (1) direct injection of the superior sagittal sinus with a radiopaque material through a catheter introduced into the sinus and (2) retrograde injection of contrast medium into a catheter introduced into the basilic vein of the arm and passed into the internal jugular vein. By using primarily the former technique we have more recently attempted resolution of the problem of so-called "pseudo tumor cerebri" and in addition studied a patient who had been submitted to radical dissection of the neck.

In the present study of venous patterns of the head and neck the patients with verified lesions of the cephalic venous outflow tract were studied by the technique of jugular venography. In this procedure iodopyracet (35 per cent) was injected directly into the jugular bulb. In addition direct injection of the jugular vein and the vertebral venous plexus permitted radiographic demonstration of venous channels in a limited number of patients.

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TECHNIQUE OF JUGULAR VENOGRAPHY

The patient is placed in a supine position with the head of the table elevated 15 degrees. A point 1 cm. below the tip of the mastoid process is identified midway between the mastoid prominence and the external auditory canal. Local anesthesia is used in the skin. A No. 18-gauge spinal needle is introduced and directed upward, posteriorly, and medially. When the base of the skull is encountered there is frequently pain. The needle is withdrawn for a few centimeters and redirected more inferiorly but still in the posteromedial direction. When the jugular bulb is entered there may not be an immediate egress of blood from the needle, but easy withdrawal of blood with a syringe establishes the position of the needle. Anteroposterior, posteroanterior, lateral, and submental roentgenograms of the skull using standard techniques are taken after each injection of 15 c.c. of 35 per cent iodopyracet (Figs. 1 and 2). There is little or no discomfort at the time of injection; however, several minutes later there may be an attack of nausea and vomiting. As much as 100 c.c. of Diodrast has been used without the production of undesirable side effects.

MATERIAL

Up to the present time 24 venographic studies have been performed on 20 patients. They were divided into the following groups: (1) those without demonstrable disease embarrassing the venous outflow from the head (9 patients), (2) those with partial to complete occlusion of the internal jugular vein by tumor (2 patients), and (3) those with surgical excision of the jugular system as done in radical dissection of the neck (9 patients).

Studies in Group I were carried out in the investigation of such problems as "pseudo tumor cerebri," carotid cavernous fistula, arterial aneurysm of the carotid system, and so forth. In Group II metastatic tumor occluded the internal jugular vein and in the other patient a tumor of the jugular bulb was the causative agent of jugular vein occlusion. In none of these were so-called "congestive changes" present. The patients in Group III had had radical dissection of the neck for carcinoma of the larynx (4 patients); carcinoma of the tongue (3 patients); carcinoma of the thyroid (1 patient); and carcinoma of the gingiva (1 patient). Eight of these individuals had unilateral dissection of the neck performed and in one bilateral operation was performed ad seriatum. There were no congestive changes in the group in which a unilateral operation was performed. Following the second stage of the bilateral procedure there was moderately severe swelling of the area drained by the jugular system. The time intervals of the studies following extirpation of the jugular system were varied. The earliest time at which venography was performed after radical neck dissection was 4 days.

PATTERN OF OCCLUSION OF JUGULAR VEIN

In the examples in which the lumen of one jugular vein had been obstructed and/or the vein removed, there were demonstrable radiographically vertebral venous channels, basilar intracranial dural sinuses, and of particular

significance was a large vein originating in a plexus at the base of the skull. This vein extended distally through the soft tissues of the neck into the thoracic inlet, presumably joining the subclavian vein. In size this channel

Fig. 1.

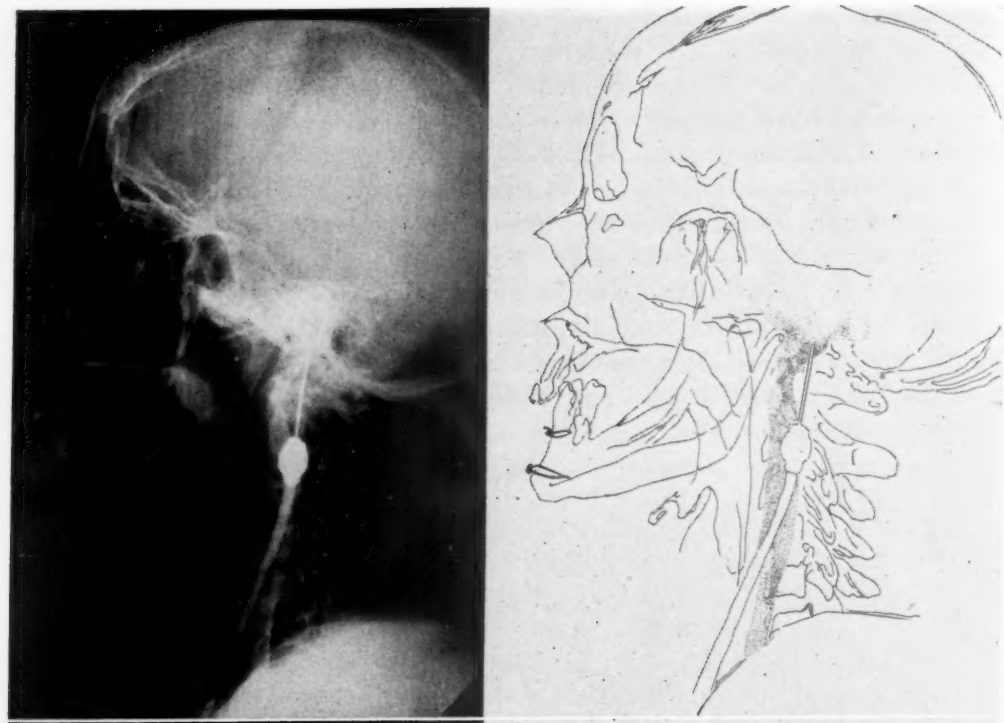

Fig. 2.

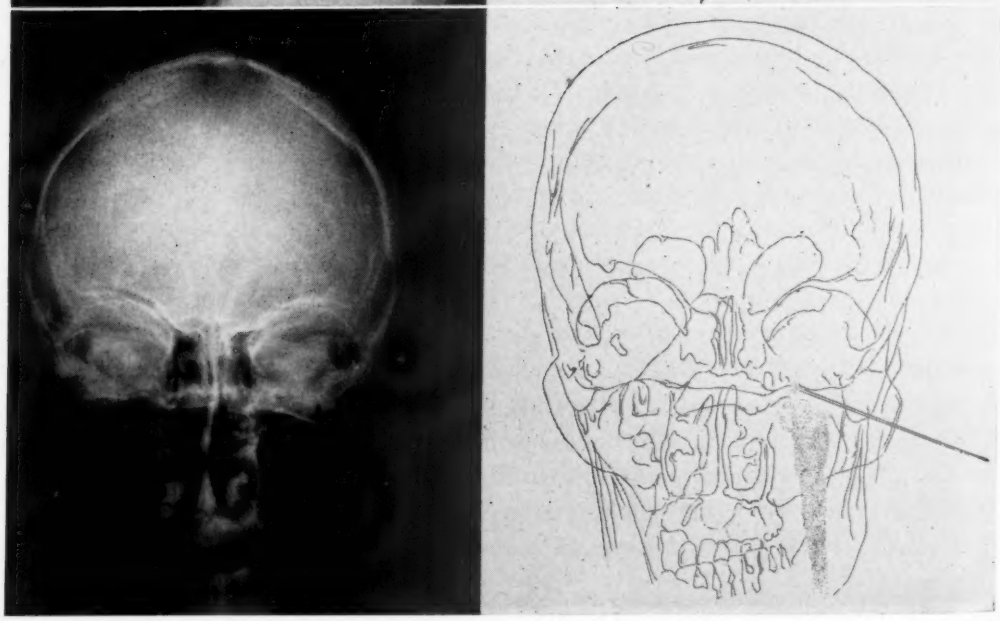

Fig. 1.—Lateral roentgenogram and tracing demonstrating position of spinal needle and normal internal jugular vein outlined by contrast medium.

Fig. 2.—Anteroposterior roentgenogram and tracing illustrating position of spinal needle in this projection as well as contour and position of normal internal jugular vein.

was approximately three-quarters the diameter of the so-called normal jugular vein. It was found to have contributions from 2 main sources, namely, the jugular sigmoidal complex via a shunt in the region of the foramen emitting the mastoid emissary vein, and the vertebral plexus. In one instance, that of a hemangiomatous pericytoma of the jugular bulb, the accessory channel from the jugular-sigmoidal complex was clearly evident at the time of surgical exposure of this area. In some cases the entire vertebral plexus was demonstrated; however, it was only from that part of the plexus between the first and third cervical vertebrae that significant contributions to the large collateral vein were evident. The accompanying illustrations help to demonstrate these features. Fig. 3 most clearly shows the course of the vertebral vein with

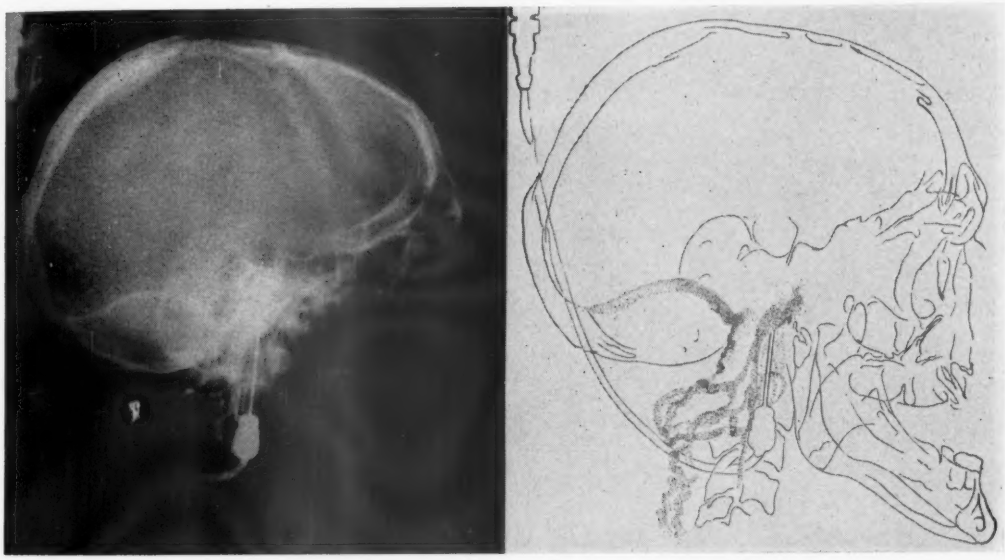

Fig. 3.—Lateral roentgenogram and tracing showing character and position of contributions of vertebral plexus to the venous shunt.

collateral channels extending posteriorly from the level of the first to second cervical vertebrae. Figs. 4 and 5 depict the contribution provided by the intracranial component with a large vein emerging through the skull from the sigmoidal sinus. Fig. 6 demonstrates the distal course through the neck of the vein formed from these 2 sources. Fig. 7 is an artist's concept of these structures based upon the x-ray findings in these cases and represents a composite drawing of the data obtained from all these examinations. It is of interest that injections of the vertebral venous plexus alone in patients without obstruction of the jugular vein permitted visualization of small collaterals which seemingly contributed to this shunt which, however, is only present in instances of occlusion of the jugular vein. Collaterals from the jugular side were also present in some patients with so-called normal jugular veins, but in none of these was a large venous shunt evident unless there was some degree of obstruction of the internal jugular vein. Irregularly the following intracranial dural sinuses were visualized: (1) homolateral sigmoid sinus, (2) one or both transverse sinuses, (3) superior petrosal sinuses, and (4) cavernous sinuses.

COMMENT

Although the technique of jugular venography has been described here as related primarily to obstructive lesions of this part of the venous system, its use has been subsequently extended to various other problems such as "pseudo tumor cerebri" and carotid cavernous fistulas. Care must be exercised, however, during the initial insertion of the needle because of the proximity of the seventh, ninth, and tenth cranial nerves. Facial paresis as well as transitory

Fig. 4.

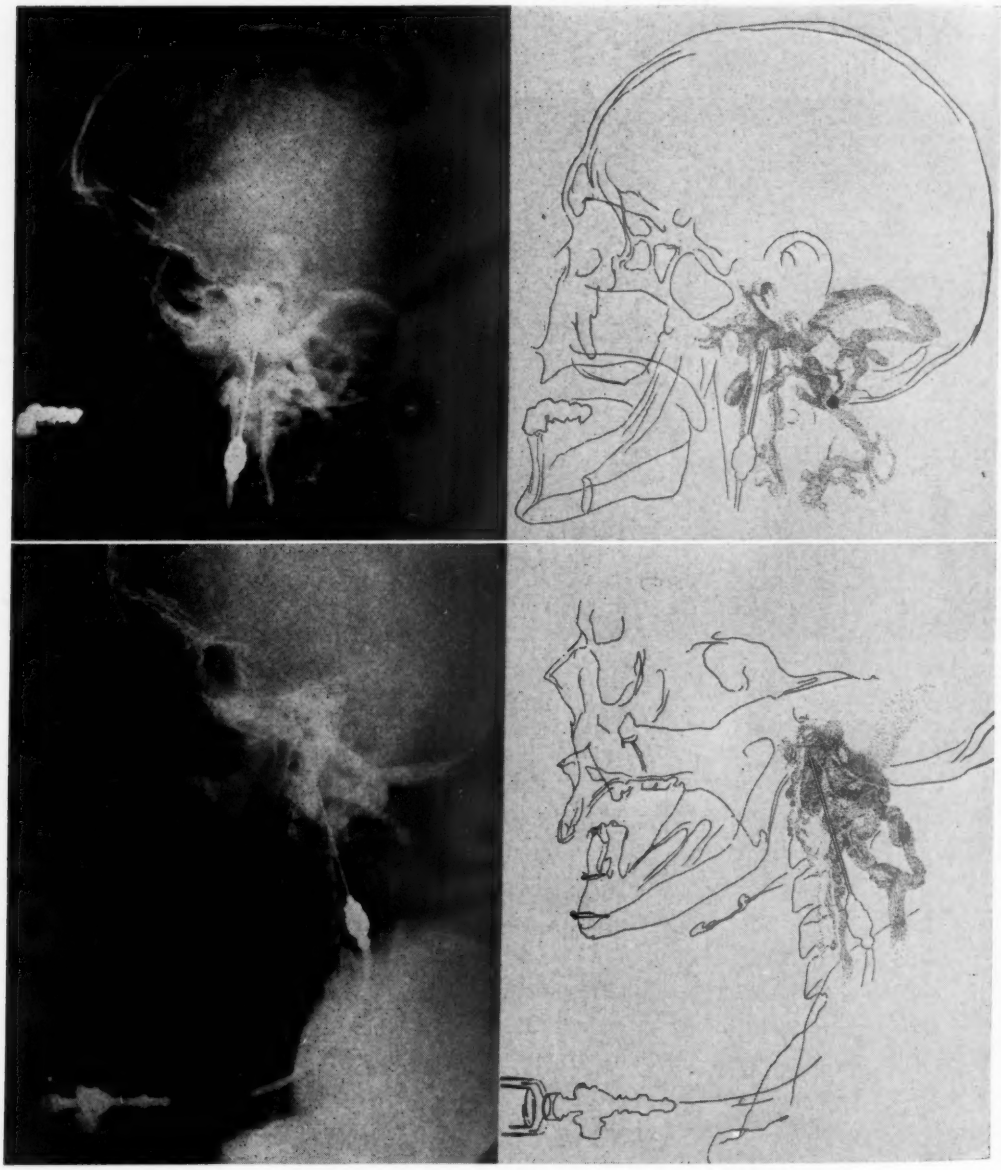

Fig. 5.

Figs. 4 and 5.—Lateral roentgenograms and tracings depicting the large collateral channel emanating from the sigmoid sinus to contribute to the deep cervical collateral vein.

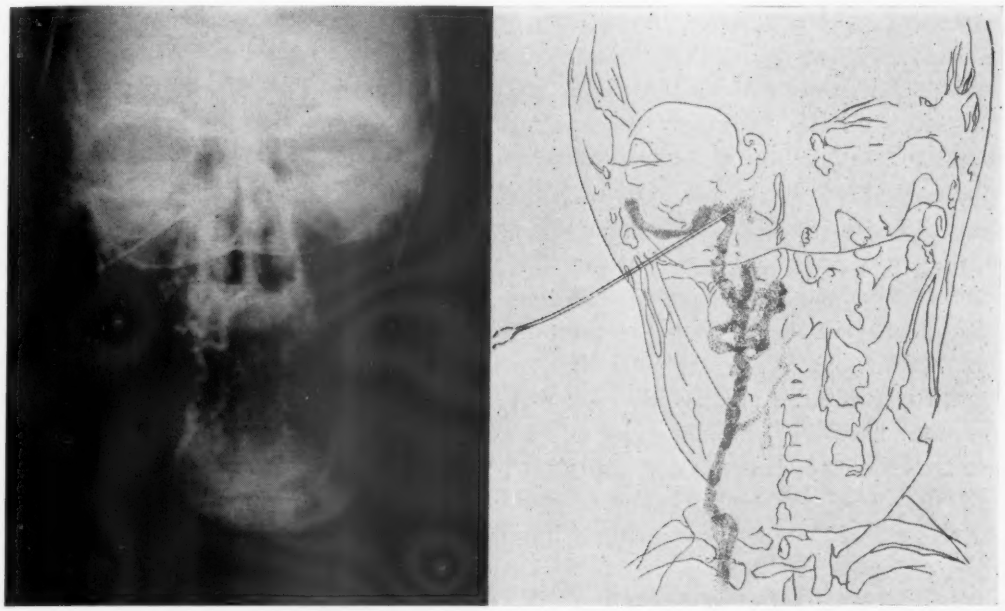

Fig. 6.—Anteroposterior roentgenogram and tracing showing the distal course through the neck of the new deep cervical collateral vein formed by the channels outlined in Figs. 3, 4, and 5.

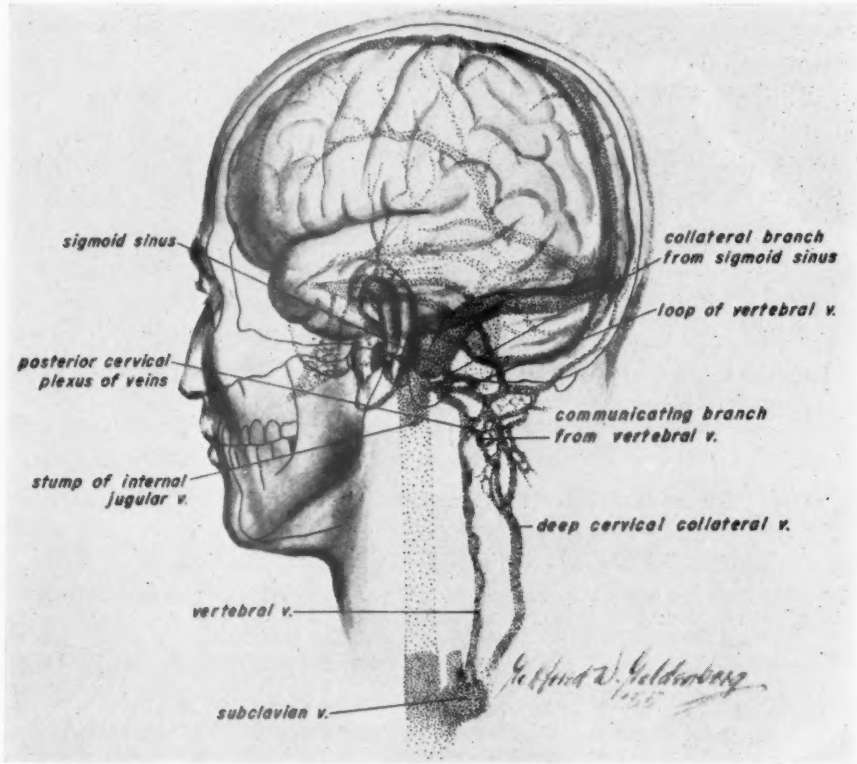

Fig. 7.—Composite drawing illustrating all special features of venous pattern following occlusion of internal jugular vein as demonstrated by jugular venography.

hoarseness has occurred. In patients in whom there was no occlusion of the internal jugular vein, this channel was portrayed as a single tube with occasional backflow into the intracranial dural sinuses (Figs. 5 and 6). In addition some of the collateral channels described as leading to the shunt were visualized in part in a few subjects, but gross connections with the vertebral venous systems were not evident. Likewise, direct injection of the vertebral venous system outlined similar small collaterals, but communications with the jugular system were not portrayed. The free communication between the jugular and vertebral venous systems and the presence of a so-called shunt existed only in instances of occlusion of one jugular vein. These data suggest that under normal conditions the vertebral and jugular systems remain as separate anatomic entities at least within the limitations of the technique employed. However, in instances of obstruction of an internal jugular vein for whatever cause, the normal collateral channels from the sigmoidal, jugular, and vertebral systems expand and develop into a large venous shunt. The constancy of this venous pattern has made possible prediction of obstruction of the jugular system prior to operation and, in one instance in particular, permitted resolution of an otherwise vague neurologic syndrome. At present the demonstration of an expanded venous circulation in the cervical area in instances of occlusion of the jugular vein seems most pertinent to problems encountered primarily in surgery of the head and neck. In the performance of unilateral dissections of the neck, signs of impaired venous drainage from the head are usually of a minimal character and transitory. However, there are a great number of individuals who require bilateral dissection of the neck either at a single operation or in stages. This is especially true for primary lesions which approach the midline in the nasopharynx, tongue, floor of the mouth, larynx, or thyroid. Following bilateral dissections of the neck, whether in one stage or two, there may be extreme swelling and cyanosis of the head accompanied by headache, papilledema, and other evidences of increased intracranial pressure. The demonstration of a collateral venous circulation in the neck following jugular vein closure suggests that functionally this may be the prime determinant of the degree of "congestive features" which follow operations of this character.

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USE OF IMPEDANCE PLETHYSMOGRAPHY IN EVALUATION OF PERIPHERAL VASCULAR RESPONSE TO ARTERIOGRAPHY

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ROENTGEN studies carried out following the intravascular injection of radiopaque media have proved to be of great value in clinical and laboratory investigation of the cardiovascular system. These studies often provide information unobtainable by other means.

The clinical injection of radiopaque media has been made most frequently into the aorta and the peripheral arterial system. The use of arteriography has contributed significantly to recent advances in the management of a number of peripheral arterial disorders by arterial replacement or bypass and these advances, in turn, have increased the demand for the use of arteriography. While arteriography may be a relatively innocuous procedure in most instances, potential hazards to its use do exist and it should be employed only to obtain information which cannot be gained by simpler measures.

One of the major problems of arteriography, as currently employed, involves the production of peripheral arterial spasm. This spasm may be quite painful in the unanesthetized patient and may, in some cases, initiate a limited period of peripheral ischemia. On rare occasions, the period of ischemia may be unusually prolonged and gangrene may occur. The peripheral vascular response to the intra-arterial injection of radiopaque media has been investigated by mechanical plethysmography in animals and patients by Jepson and Simeone[3] and in patients by Shaw.[7] It has been studied through the assessment of spinal cord and renal damage in intra-aortic injection by Grimson and his associates.[2, 8]

In this investigation, impedance plethysmography was employed to study the peripheral vascular response in experimental arteriography. The impedance plethysmograph was, with slight modification, the one used in the clinical study of a variety of vascular disorders as reported from this laboratory in 1952 by Coxe, Shumacker, and Freeman.[1] The impedance plethysmograph records the same alterations in digital volume as the mechanical plethysmograph. The recorded oscillations produced by these alterations in digit volume are regarded as reflecting with reasonable accuracy the character of digital pulse volume.

The biophysical background of tissue impedance and impedance plethysmography is discussed in detail in the publications of Nyboer and his associates.[4-6] In brief, the electrical impedance of a body segment is a function of the volume of the part and its electrical conductivity is directly proportional to its

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physical volume change. The impedance plethysmogram is a recording of variations in the electrical resistance and reactance of a segment of the body to intermediate and high frequency alternating current and the tracing, accordingly, is regarded as reflecting the mechanical pulse volume changes which produce the alterations in electrical resistance and reactance of the part.

APPARATUS AND METHODS

The impedance plethysmographic apparatus used in this study was only slightly modified from the one pictured and described in detail in the report of Coxe and his associates.[1] The modifications were made by Mr. Robert Crawford who was in constant attendance throughout this investigation as electronics advisor. A Sanborn Poly-Viso Cardiette was employed for direct writing recording.

Healthy mongrel dogs were used. Intravenous Pentothal was employed for anesthesia and an endotracheal tube was secured in place to insure an adequate airway. The studies were carried out in a constant temperature room in which the temperature was maintained at 20° C. and the humidity at 50 per cent. A period of time was allowed for the animals to reach thermal stability for the environment.

One hind paw and the inner aspect of both thighs were shaved. Two circumferential copper band electrodes were taped to the shaved paw of the dog, one approximately 2 cm. above the other. In the operation of the plethysmograph, a current is impressed upon the paw through one of the circumferential electrodes. It is picked up by the other circumferential electrode but is balanced out to zero by the plethysmograph. Any change in the reactance of the segment upsets this zero balance and is amplified on the recording device to produce the pulse tracing.

The femoral artery of the hindlimb attached to the plethysmograph was exposed by careful dissection in the upper portion of the thigh and a fine silk ligature was passed under it for traction purposes, when necessary. A No. 20 or 23 gauge needle, attached to a 10 c.c. syringe containing one of the solutions to be studied, was inserted into the lumen of the artery in a distal direction and injection was carried out. The needle was left in place and only the syringe was changed for subsequent injections.

Control plethymographic tracings were made prior to any arterial manipulation. Tracings were made during the various injections and throughout the periods between injections. In a number of the experiments, a polyethylene tube containing some normal salt solution and heparin was introduced into the contralateral femoral artery and was passed cephalad. The tube was attached to a pressure transducer for simultaneous recording of the contralateral arterial pulse pressure in an effort to differentiate between local and systemic factors involved in any recorded changes in the plethysmographic tracings.

The radiopaque media studied were Diodrast, Urokon, and Renografin. The effect of procaine and Priscoline on the spasm produced by these media also was investigated.

RESULTS

Tracings suitable for analysis were obtained in injection experiments in 14 animals. While some variance in the character and intensity of response to the

radiopaque media was noted, a number of the reactions were observed to occur repeatedly. To illustrate some of these findings, impedance plethysmographic tracings from 7 experiments will be presented in some detail and the significance

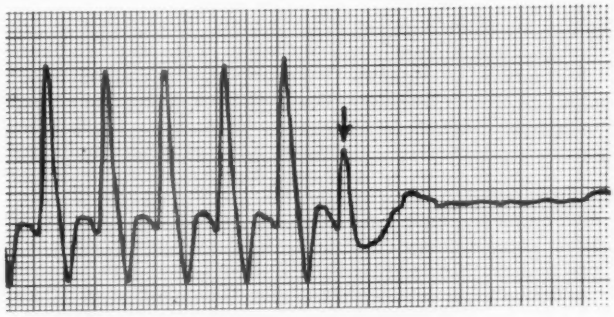

Fig. 1.—Impedance plethysmographic tracing demonstrating the effect of sudden proximal arterial occlusion (arrow).

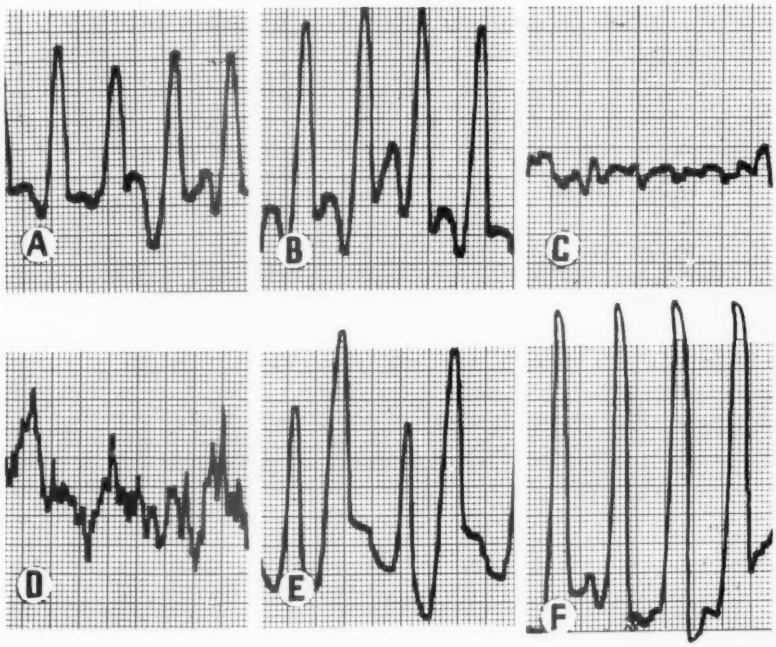

Fig. 2.—Tracings taken during studies on Dog. 1. Control tracing is shown in *A*. *B* is taken during injection of 5 c.c. of normal salt solution. Effect of first injection of 5 c.c. of 70 per cent Urokon is shown in *C* and that of second injection of 5 c.c. of 70 per cent Urokon in *D*. Tracing in *E* is made immediately after injection of 5 c.c. of 70 per cent Urokon diluted to 13 c.c. with whole blood and that in *F* is made at the time of the fourth injection of 5 c.c. of 70 per cent Urokon.

of these observations discussed. In evaluating the effect of injection-induced arterial spasm on the reduction of plethysmographic oscillations, it is of interest to compare these findings with the abrupt elimination of oscillations produced by acute proximal arterial occlusion (Fig. 1).

Dog 1.—In this animal, the effects of a control injection of normal salt solution and of repeated injections of 70 per cent Urokon were studied (Fig. 2). Normal salt solution (5 c.c.) was injected with moderate rapidity through a No.

20 gauge needle. No spasm was noted at the time of arterial puncture or injection. The magnitude of the plethysmographic oscillations increased to a small degree during the injection and for a short time thereafter, following which they returned to the control levels.

The first of the four 5 c.c. injections of 70 per cent Urokon then was carried out. Severe and relatively prolonged arterial spasm with marked reduction in plethysmographic oscillations occurred. These injections generally were accompanied by significant momentary striated muscle spasm as well. The period required for recovery of significant oscillations was approximately 4 minutes. The spasm following the second 5 c.c. injection was slightly less severe and the recovery period following injection was less prolonged. Oscillations had recovered in approximately one minute and were observed to be at a slightly higher level than during an equivalent period in the recovery phase after the first injection. In the third injection, the 5 c.c. of 70 per cent Urokon was diluted to 13 c.c. with whole blood prior to injection. There was no spasm at the time of injection and some increase in the magnitude of oscillations was observed in the postinjection period. In the fourth injection, 5 c.c. of 70 per cent Urokon was injected without dilution. This injection produced a vasodilating effect with an increase in the amplitude of the oscillations.

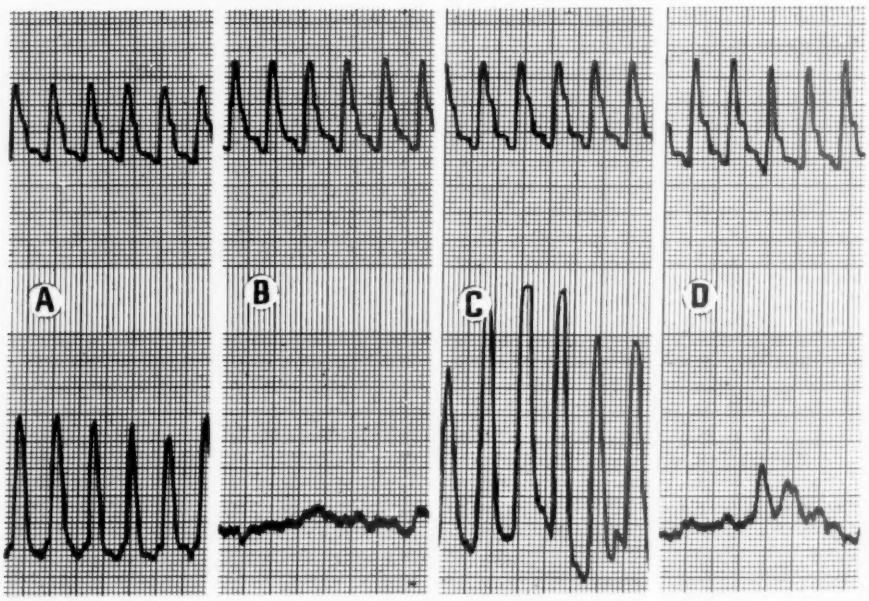

Fig. 3.—Simultaneous recording, in Dog 2, of plethysmographic tracings (*lower*) and arterial pulse pressure in contralateral limb as recorded through a transducer (*upper*). Control tracings are shown in *A*, effect of acute proximal arterial occlusion in *B*, very transient initial vasodilatation during injection of 10 c.c. of 70 per cent Urokon in *C*, and marked and prolonged vasospasm immediately following the injection in *D*.

Dog 2.—In this animal, the occurrence of initial vasodilatation followed promptly by marked vasoconstriction with injection of 10 c.c. of 70 per cent Urokon was illustrated (Fig. 3). Arterial pulse pressure from the contralateral limb was recorded simultaneously through a transducer. Acute proximal arterial occlusion eliminated the plethysmographic oscillations and produced no

change in the contralateral pulse pressure. The initial response of the peripheral arterial circulation to the Urokon during the injection was one of vasodilatation. However, this vasodilatation was quite transitory and, by the completion of the injection, pronounced vasoconstriction with significant reduction in plethysmographic oscillations had occurred. Relatively little pulse pressure change was associated with the marked alterations in the plethysmographic tracings.

Dog 3.—The reduced vasoconstriction effect of a smaller injection of 70 per cent Urokon and its capacity to mitigate the spasm of a subsequent larger injection was studied in this animal (Fig. 4). Considerably less spasm and reduction in plethysmographic amplitude was observed when 3.5 c.c. of Urokon was injected. Second and third injections of 5 c.c. of Urokon produced greater spasm but less than when these injections were given initially. The spasm of the third injection was less than that associated with the second. Even less reduction in amplitude was noted when 5 c.c. was given in the fourth Urokon injection. An increase in amplitude was found in the recovery phase following each injection. This increase appeared to be of the greatest magnitude following the last injection.

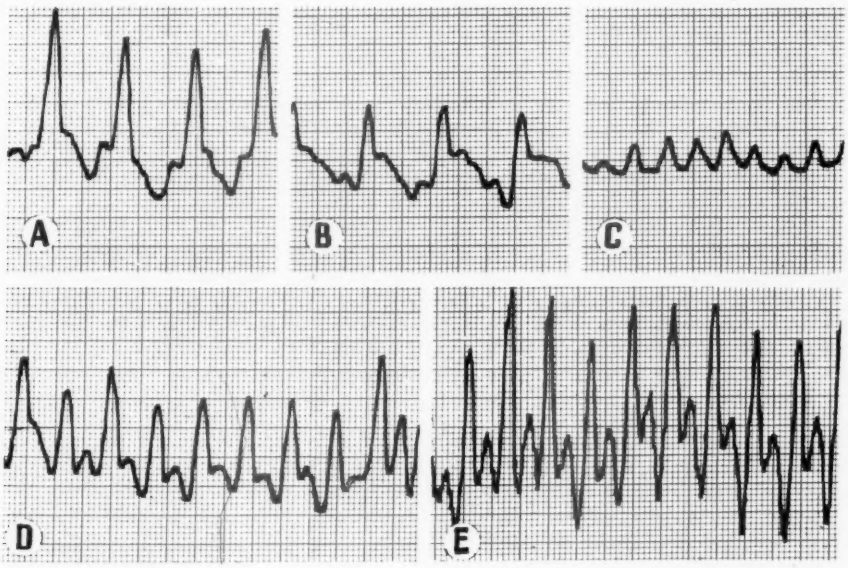

Fig. 4.—Tracings in Dog 3 showing control oscillations (*A*), relatively mild vasospastic effect of 3.5 c.c. of 70 per cent Urokon (*B*), greater vasospasm following second 70 per cent Urokon injection, 5 c.c. (*C*), less spasm at completion of third 70 per cent Urokon injection, 5 c.c. (*D*), and increase amplitude of oscillations in recovery phase following the third injection (*E*).

Dog 4.—A reduction in vasospasm with multiple repeated injections of 50 per cent Urokon was shown in this animal (Fig. 5). The failure of the central systemic arterial pulse pressure to change indicated that this decreasingly vasospastic response was a local one. Ten cubic centimeters of 50 per cent Urokon was given in each of the first 3 injections. The spasm was less severe and less prolonged after each repeated injection. No spasm and, indeed, some increase in amplitude of oscillations were encountered with the fourth injection. Similar findings were observed with the fifth, sixth, and seventh injections.

Dog 5.—In this animal, the failure of Priscoline to protect against the occurrence of vasoconstriction when given as a combined injection with Urokon was demonstrated (Fig. 6). Ten cubic centimeters of 70 per cent Urokon and 10 mg. of Priscoline were mixed and injected. The peripheral vasospasm and

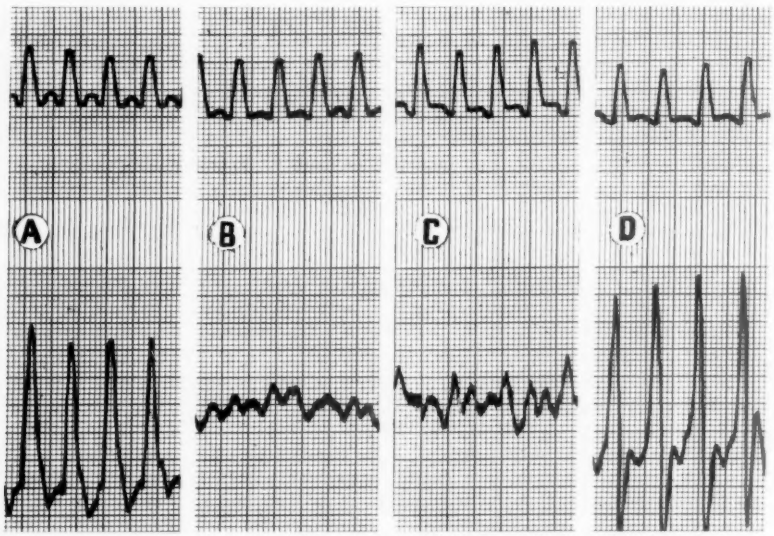

Fig. 5.—Simultaneous recordings of contralateral limb pulse pressure (*upper*) and plethysmographic tracings (*lower*) in Dog 4. Control tracings are shown in *A*. Decreasing vasospasm with repeated injections is illustrated. Vasospasm following first injection of 10 c.c. of 50 per cent Urokon is shown in *B* and that following second injection of identical amount in *C*. Increase in amplitude of oscillations is observed immediately following fourth 50 per cent Urokon injection of 7 c.c. in *D*.

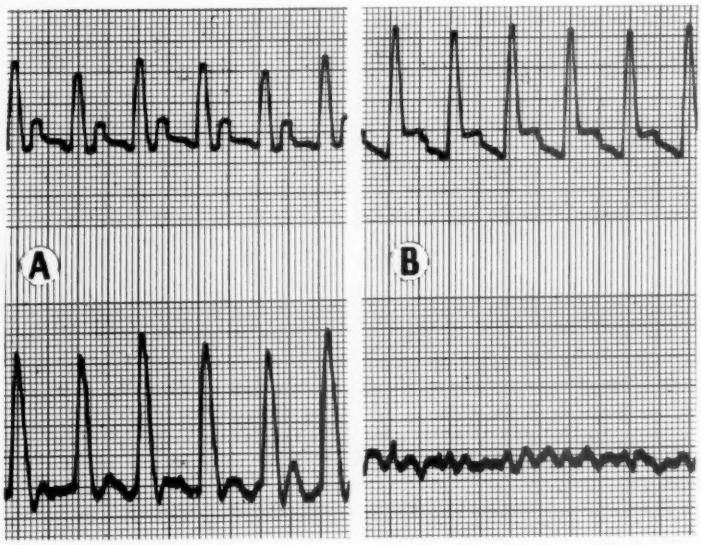

Fig. 6.—Simultaneous recording of contralateral limb pulse pressure (*upper*) and plethysmogram (*lower*) in Dog 5. Effect on control tracing (*A*) of injection of mixture of 10 c.c. of 70 per cent Urokon and 10 mg. of Priscoline is one of marked and prolonged vasospasm (*B*).

striated muscle spasm were accompanied within a short period of time by generalized convulsion. The peripheral vasospasm was severe and unusually prolonged despite the occurrence, duing this period, of an increase in the systemic arterial pulse pressure as recorded through the transducer.

Dog 6.—The relatively mild vasospastic response to Renografin and the capacity of repeated Renografin injections to protect against Urokon-induced vasospasm was investigated in this animal (Fig. 7). Surprisingly little spasm and reduction in amplitude of oscillations were produced by the injection of 5 c.c. of 47.8 per cent Renografin. Even less spasm was associated with the

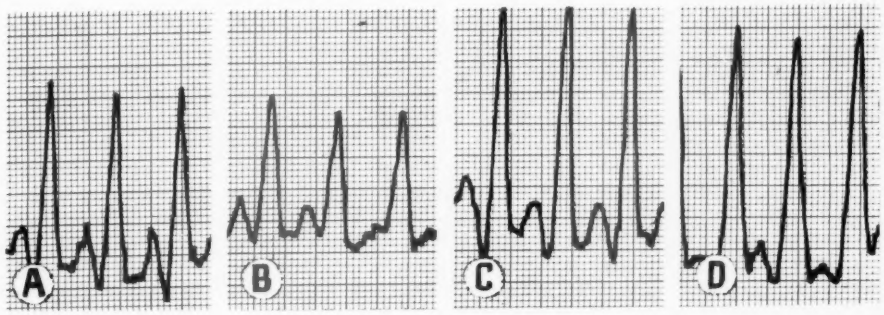

Fig. 7.—Plethysmographic tracings from Dog 6 showing the relatively mild vasospastic effect (*B*) of an injection of 5 c.c. of 47.8 per cent Renografin on the control oscillations (*A*). An increase in the amplitude of oscillations one minute after second 5 c.c. Renografin injection is observed in *C*. Protective effect of 3 Renografin injections on subsequent injection of 10 c.c. of 70 per cent Urokon is illustrated in *D* by the good amplitude of oscillations following injection.

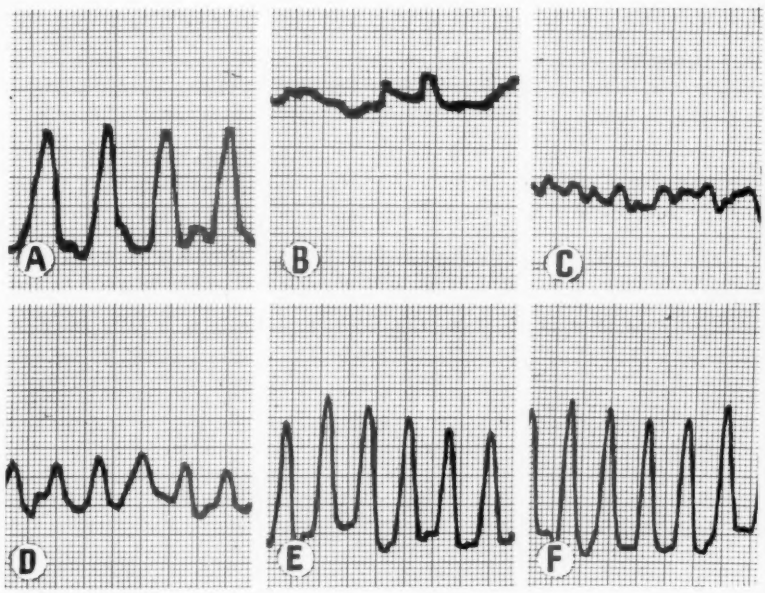

Fig. 8.—Tracings from Dog 7 demonstrating the protective effect of intra-arterial procaine injection. Control tracing is shown in *A*. Marked vasospasm followed the injection of 10 c.c of 35 per cent Diodrast (*B*) and a second injection containing 10 c.c. of 35 per cent Diodrast and 3 c.c. of 1 per cent procaine (*C*). The degree of persisting arterial spasm just prior to the injection of 10 c.c. of 1 per cent procaine is shown in *D*. The procaine injection was followed by an increase in the amplitude of oscillations (*E*). Injection of 10 c.c. of 35 per cent Diodrast carried out a short time after the procaine injection produced no change in the amplitude of oscillations (*F*).

second injection of 5 c.c. A significant increase in amplitude was observed approximately one minute following the second injection. The third injection of 5 c.c. of Renografin produced no change in the tracing. Approximately 3

minutes later, 10 c.c. of 70 per cent Urokon was injected. Although some striated muscle spasm occurred, there was no significant arterial spasm. The amplitude, one minute after the injection, was excellent.

Dog 7.—The vasospastic response to Diodrast and the protective effect of prior injection of procaine were demonstrated in this animal (Fig. 8). The simultaneous injection of Diodrast with a smaller amount of procaine had failed to protect against the occurrence of vasospasm. A considerable degree of arterial spasm was produced by the injection of 10 c.c. of 35 per cent Diodrast. Only slightly less spasm occurred with the injection of a mixture of 10 c.c. of 35 per cent Diodrast and 3 c.c. of 1 per cent procaine. Although some recovery of the amplitude of oscillation took place in the period after the second injection, a degree of arterial spasm persisted. This spasm was relieved by the injection of 10 c.c. of 1 per cent procaine. A short time after the procaine injection, 10 c.c. of 35 per cent Diodrast was again injected. This time there was no change in the plethysmographic tracing. One additional Diodrast injection was made and this also was free of vasospastic response.

DISCUSSION

Some variation in the clinical response to intra-arterial Diodrast and Urokon was shown in 1956 by Shaw. Mechanical plethysmography was carried out by him during lower extremity arteriography in 15 patients. Three patterns of response were observed. In 10 patients, there was an immediate decrease in oscillations, indicating complete or near complete disappearance of the pulse. This decrease lasted from 1 to 6 minutes and was followed by an increase in oscillations above the original level. In 3 patients, the decrease in oscillations was observed but it was not followed by an increase above the original level. An increase in oscillations was observed in 2 patients without evidence of vasoconstriction. The vasoconstriction occurred in all of the 3 patients who had had prior sympathectomy, suggesting that this response is largely a local one and independent of the sympathetic nervous system.

Jepson and Simeone,[3] in 1953, employed a mechanical type of plethysmograph to study the peripheral response to the injection of Diodrast, sodium iodide, and Thorotrast into the femoral artery in 9 dogs. Injections were relatively small, in the 1 to 4 c.c. range. They observed either no change in oscillations or a vasodilatation which, at times, was preceded by a brief vasoconstriction. In the 3 patients studied by them, vasoconstriction was more pronounced. Sympathectomy in 3 dogs did not appear to alter the character of the response.

The production of spinal cord lesions with Urokon aortography in dogs was described by Tarazi, Margolis, and Grimson[8] in 1956. The injury presumably resulted from vasospastic cord ischemia. Fifteen cubic centimeters of 70 per cent Urokon had been injected into the aorta near a radicular artery. In a recent study, Huger, Margolis, and Grimson[2] found that intra-aortic injection of 1 c.c. of 70 per cent Urokon per kilogram, with balloons inflated in the aorta above and below the renal arteries at the time of injection, produced severe nephrosis in each of 7 dogs. Intra-aortic injection of Priscoline, 2 c.c. per kilogram, 1 or 2 minutes prior to injection of the Urokon did not minimize renal

damage in 6 dogs. On the other hand, preliminary injection of procaine, 25 mg. per kilogram, prevented serious renal damage in 8 of 9 dogs. There was no protective effect in the simultaneous injection of Urokon and procaine.

The peripheral vascular response in this study to the initial intra-arterial injection of radiopaque media, in general, fitted in well with these reported observations. The response to the larger injections of media in this study was rather consistently one of vasospasm. The impedance plethysmograph was found to be a useful apparatus for the recording and evaluation of this response experimentally in dogs. Repeated injections of the same amount of media produced progressively less vasospasm and the duration of spasm was shorter. Varying degrees of vasodilatation occurred in the recovery periods between injections. The amplitude of oscillations during these periods often appeared to increase with repeated injections. By the time the fourth injection was carried out, the response frequently was one of no vasoconstriction or even of some mild degree of vasodilatation.

In a single animal, the initial injection was associated with a brief increase in the amplitude of the oscillations followed promptly by the period of vasospasm. The needle puncture of the artery did not produce demonstrable vasoconstriction in any of the animals studied. Control injections of normal salt solution and of whole blood also caused no vasospasm. Injection of these substances produced either no change or a slight increase in the amplitude of the plethysmographic tracings.

In contrast, when smaller amounts were used, vasodilatation often accompanied the injection. It also was of interest that repeated small, nonspasm-producing injections of media tended to protect against the severe vasospasm of a subsequent larger injection. The protection thus afforded appeared to involve not only the medium injected in repeated small amounts but other media as well.

The most severe and prolonged vasospasm occurred with the injection of 70 per cent Urokon. In general, of the 3 radiopaque media investigated, Renografin seemed to produce the least marked peripheral vasoconstriction on intra-arterial injection.

That these recorded peripheral vascular responses in the injected limb were essentially local in character was suggested by the absence of any change in the pulse pressure of the contralateral limb as recorded simultaneously through a transducer in a number of the experiments.

Priscoline, injected with the radiopaque medium, did not protect against the development of severe vasoconstriction. Although procaine did not have a protective effect when injected with the medium, its intra-arterial use did appear to have a beneficial effect upon already existing spasm, leading to an increase in the amplitude of oscillations. Our limited observations suggested that the prior intra-arterial injection of procaine protected against the vasospasm which might otherwise be expected from a subsequent injection of radiopaque medium.

Thus, the radiopaque media studied appeared to have a vasodilating effect in small or dilute amounts and a vasoconstrictor effect in larger volumes and

greater concentrations. The vasoconstrictor effect becomes less marked in intensity and duration with repeated injections. The effect seems to be a local one and is not affected by Priscoline or sympathetic denervation of the limb. Only preliminary intra-arterial injection of procaine and repeated small injections of the media appear to protect against its occurrence.

In view of these observations, it would be wise, in carrying out arteriography, to limit the volume and concentration of radiopaque media to the smallest amount which will provide adequate visualization. Furthermore, this method of study should be employed only to gain essential information not obtainable by simpler and safer means. There is evidence to suggest that the preliminary injection of procaine may protect against the production of potentially hazardous peripheral vasoconstriction by the media and its clinical trial would seem justified. It would also be interesting to see whether or not in patients, as in animals, repeated small injections of medium prior to the main injection might be of value not only to test for possible drug sensitivity but also to exert a protective effect in limiting the severity of the vasoconstrictor response.

SUMMARY

1. The literature pertaining to the peripheral vascular response to intra-arterial injection of radiopaque media is reviewed briefly.

2. The experimental use of impedance plethysmography in the evaluation of the peripheral arterial response to arteriography in dogs is reported.

3. Relatively large injections of radiopaque media consistently produced vasospasm. With repeated injections, both the degree and duration of the vasoconstriction became progressively less until either no response or mild vasodilation resulted.

4. In the recovery phase between injections, the amplitude of oscillations frequently exceeded the control or preinjection levels.

5. In small amounts and dilute concentrations, the media tended to cause vasodilatation. Repeated injections of small, nonspasm-producing amounts of media appeared to protect against the severe spasm of a subsequent larger injection.

6. Intra-arterial injection of Priscoline did not protect against the occurrence of vasospasm when spasm-producing amounts of media were injected.

7. A protective effect against the vasospasm of arteriography was observed with the prior intra-arterial injection of procaine. The success of intra-arterial injection of relatively large amounts of procaine in reducing pre-existing, media-induced vasoconstriction also was noted.

8. The essential local character of these vascular responses was indicated by the absence of any significant change during these studies in the systemic pulse pressure as recorded from the contralateral limb through a transducer.

9. The effect of Diodrast, Urokon, and Renografin was investigated. Of the three, Renografin appeared to produce the least amount of peripheral vasospasm in the volumes and concentrations employed.

10. Possible clinical applications of these observations are discussed.

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ATHEROSCLEROTIC CHANGES IN GRAFTS OF THE THORACIC AORTA

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AN IDEAL arterial replacement should have the following attributes: (1) ease of suture, (2) low tissue reactivity, (3) a degree of porosity, especially for replacement or bypass of vessels smaller than the aorta,[4] and (4) resistance to degenerative changes over prolonged periods of time. The latter is the concern of the work to be presented. Heterologous grafts from hog to man, or from hog to dog, have proved unsatisfactory, because these grafts very rapidly undergo extensive degeneration with deposition of calcium within the arterial wall and eventual aneurysm formation.[2] Homologous arterial grafts are known to have calcified following insertion into the thoracic aorta, at a time when the host aorta did not demonstrate this degenerative change.[5]

The present investigation was designed to determine the differences in atheromatous degeneration in 4 types of arterial replacement in the dog with induced hypercholesterolemia. Creech and co-workers[2] have demonstrated that arterial homografts in the abdominal aorta distal to the renal vessels quickly undergo atheromatous degeneration under these conditions. Very recently Creech and co-workers[3] have shown that 2 synthetic aortic substitutes at the same site and under similar circumstances undergo few degenerative changes.

METHODS

A total of 34 arterial grafts of nylon, Orlon, Ivalon, and homografts were placed in the thoracic aorta of 21 adult mongrel dogs. The grafts were placed either singly or in multiples of 2 or 3 different substances. Five of the grafts were Orlon, 6 nylon filter fabric, 12 compressed Ivalon, and 11 were fresh homografts preserved in Tyrode's solution. Following recovery from the operative procedure the animals were given radioactive iodine in a dosage of 4 millicuries per kilogram of body weight intravenously and were force fed 10 Gm. of purified cholesterol, suspended in corn oil, daily by means of gastric gavage, in addition to a regular diet. A similar method of producing arteriosclerosis in dogs was introduced by Steiner and associates.[8]

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Base line serum cholesterol determinations were performed prior to initiation of cholesterol feedings and monthly thereafter. The dogs were weighed monthly. The cholesterol feedings were continued for an average of 49 weeks and the grafts were in place for an average of 77 weeks. At the end of this time the dogs were sacrificed and the heart and entire aorta were removed for gross and microscopic examination. All grafts were graded independently by the observers and rated from 0 to 4. A graft which showed no evidence of ulceration or pigment deposition and was completely smooth was represented by 0; 1+ was awarded to grafts which had pigment deposition with slight roughening of the lining; 2+ represented a graft with a roughened lining and pigmented plaques which were elevated and discrete; 3+ represented those grafts which had pigment deposits, a small thrombus, or small ulceration; and 4+ was awarded to those grafts which exhibited gross ulceration or degeneration with plaques with or without calcification. Thus a lower numerical order represented a better result from the standpoint of atheromatous degeneration. Excellent agreement existed when the independent evaluation of the 3 observers was compared.

Two of the grafts (Orlon and Ivalon in the same animal) were completely occluded and were excluded from the evaluation since the occlusion was the result of infection and thrombus formation and not related to atheromatous degeneration.

To determine whether cholesterol was deposited in the aortic substitutes and to corroborate, if possible, the gross classification, tissue cholesterol determinations[6] were performed on all grafts at the time of sacrifice. Microscopic slides were prepared and stained with hematoxylin and eosin. Sudan IV preparations were made on frozen sections.

RESULTS

The mean base line serum cholesterol prior to initiation of cholesterol feeding was 162.5 mg. per cent (range 116 to 193 mg. per cent). The highest serum cholesterol determination after cholesterol feeding was 910 mg. per cent. The average of all serum cholesterol determinations after feedings were begun was 403.9 mg. per cent, an increase of 2.5 times the control. The average for the final 3 months of cholesterol feeding was 460 mg. per cent. The elevation of serum cholesterol was not great on the average and within the range quite commonly observed in humans. On this regimen the animals gained an average of 14.5 pounds (range –2 to 31 pounds).

At this level of hypercholesterolemia the host aortas were practically free of atheromatous change. All aortic substitutes evaluated showed greater vulnerability to atheromatous change than the host aorta. The details of this evaluation together with serum and tissue cholesterol values appear in Table I and Fig. 1. The best replacements were Orlon and nylon which were much better from all standpoints of evaluation than the homograft or Ivalon.

The average gross classification for the host aorta was 0; for Orlon 0.75; for nylon 1.33; for the homografts 2.45; and for Ivalon 2.8.

TABLE I. CHEMICAL AND PATHOLOGIC DATA ON DOGS WITH AORTIC HOMOGRAFTS AND SYNTHETIC GRAFTS

DOG NO.	AVERAGE SERUM CHOLESTEROL AFTER CHOLESTEROL FEEDINGS BEGUN	LAST 3 MONTHS OF STUDY (MG. %*)	TISSUE CHOLESTEROL					GROSS CLASSIFICATION†					TIME BETWEEN GRAFT AND SACRIFICE (MONTHS)
			HOST AORTA	HOMO-GRAFT	IVALON	ORLON	NYLON	HOST AORTA	HOMO-GRAFT	IVALON	ORLON	NYLON	
85	323	315	1.6	10.7	11.4	3.7	–	0	+++	++	+	–	22
491	584	206	1.8	–	1.5	–	–	0	–	+++	–	–	20
615	339	389	1.7	–	1.4	–	–	–	–	++++	0	–	23
647	338	359	1.9	7.7	3.5	1.5	–	0	+	+++	+	–	21
709	385	429	1.6	3.2	–	–	–	0	++++	–	–	–	19
741	256	264	2.2	–	6.3	–	2.5	0	–	++	–	0	17
744	423	550	2.0	2.2	–	–	–	0	+	–	–	–	18
746	263	273	2.0	–	4.1	2.2	2.5	0	–	++++	+	++	19
747	544	628	2.0	6.9	–	–	–	0	++++	–	–	–	18
749	293	347	2.4	1.9	–	–	–	0	++++	–	–	–	19
755	536	637	2.3	5.6	–	–	–	0	++	–	–	–	18
817	564	725	2.3	2.8	–	–	–	0	++	–	–	–	16
803	305	345	2.0	–	2.4	–	2.3	0	–	+++	–	++	14
612	434	457	1.9	–	–	–	–	0	–	+++	–	–	20
820	584	841	2.1	–	–	–	–	0	–	++	0	0	16
748	381	410	–	–	–	–	–	–	+++	–	–	–	19
751	271	252	–	–	–	–	–	–	++	–	–	–	14
772	529	540	–	–	–	–	–	–	–	–	–	++	13
790	418	482	–	–	–	–	–	–	–	++	–	++	13
798	328	303	–	–	–	–	–	–	+	–	–	–	16
Normal dogs			1.6										
Average			1.9	5.1	4.4	2.5	2.4	0	2.45	2.8	0.75	1.33	

*Base line average of all dogs before cholesterol feeding 162.5 (116 to 193) mg.%.
†See text for basis of classification.

The tissue cholesterol determinations supported the gross classification. The average tissue cholesterol on normal dog aorta is 1.6 ± 0.3 mg. per gram; on host aorta (hypercholesterolemic dogs) 1.9 mg. per gram; on nylon grafts 2.4 mg. per gram; on Orlon grafts 2.5 mg. per gram; on Ivalon 4.4 mg. per gram; and on homografts 5.1 mg. per gram (Fig. 2).

Microscopic study of the grafts revealed a lining membrane, covering the whole inner surface of the graft material. The roughened and thickened areas were seen to be composed of fibrin thrombi and were the site of yellow pigmented, amorphous deposits and of deposits of an unidentified fat. No foam cells were found in any of the grafts. Calcification was seen in some of the homografts. Fat stains using Sudan IV were prepared. Cholesterol is not sudanophilic and was not recognizable as such. In some of the graft substances, notably Orlon, many small sudanophilic fat globules were seen. The latter were not recognized on the hematoxylin and eosin preparations.

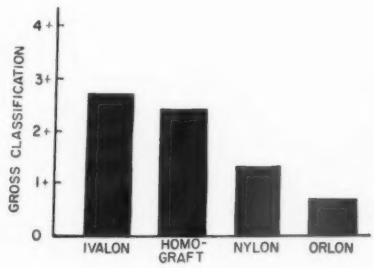

Fig. 1.

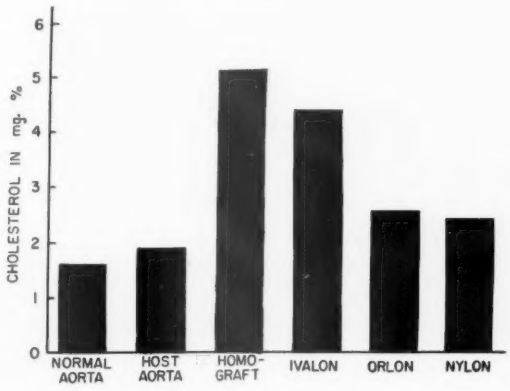

Fig. 2.

Fig. 1.—Evaluation of degenerative changes in aortic grafts.
Fig. 2.—Tissue cholesterol in normal aorta, host aorta, and graft replacements.

DISCUSSION

The results of this investigation show that marked atheromatous degeneration of homografts and Ivalon occurs in animals with only moderate elevation of serum cholesterol. Grafts of Orlon and nylon, while more vulnerable than the host aorta, are much more resistant to atheromatous degeneration than Ivalon or a homograft. The method of placing 2 or 3 materials in series as an aortic replacement in a single dog allowed one to compare the degenerative processes in grafts under almost identical conditions.

The gross degenerative change in homografts appears to occur as readily in the thoracic aorta (this study) as in the abdominal aorta (Creech and associates[2]). Turbulence and other mechanical factors have been implicated in the atheromatous degeneration noted maximally in the distal aorta in humans and in experimental animals exposed to high cholesterol diets.[1]

The elevation of serum cholesterol was not related to the extent of graft degeneration nor to the elevation of graft tissue cholesterol over the range studied. Some animals with a comparatively low blood cholesterol had 4+

changes in the graft, whereas other animals with consistently high blood cholesterol levels had 1+ alterations. The average blood cholesterol of those animals which received homografts or grafts of Ivalon was not greater than in those animals in which Orlon and Nylon were implanted, nor was the feeding period consistently different. When multiple grafts existed in the same animal, the gross degenerative changes and tissue cholesterol were greater in the Ivalon and homograft than in the Orlon and nylon. The increased incidence of atherosclerotic changes in the Ivalon grafts and homografts is possibly due to the larger amount of foreign body implanted, rather than to any intrinsic difference in the reaction of the host to the material.

Biochemical investigation of the human aorta with atheromatous change by Noble and associates[7] revealed that total lipid is increased in the intima in both males and females. However, only in the male is the increase due to cholesterol. In the female other lipids are responsible for the elevation of the total. In the present study only 3 of the dogs were female and the tissue cholesterol was not significantly different in the graft and the host aorta in these animals. Further investigation on this sex difference would be of interest.

SUMMARY AND CONCLUSIONS

1. An atherogenic diet which caused a moderate increase in serum cholesterol in dogs (average 404 mg. per cent with normal 162 mg. per cent) resulted in severe atheromatous degeneration in aortic graft replacements of Ivalon and homografts. Minimal degeneration occurred in grafts of nylon and Orlon. On gross evaluation of the grafts and rating from 0 to 4 on the basis of increasing atheromatous change, the host aorta was 0; Orlon 0.75; nylon 1.33; homografts 2.45; and Ivalon 2.8. All grafts were placed in the thoracic aorta.

2. The induced hypercholesterolemia (less than 1,000 mg. per cent) had no observed effect upon the host aorta over the period of study (average cholesterol feeding period 49 weeks).

3. The degree of degeneration as assessed by observation of pigmentation, ulceration, calcium deposition, and plaque formation was not correlated with the elevation of serum cholesterol or tissue cholesterol over the range studied (150 to 900 mg. per cent).

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EXPERIMENTAL PRODUCTION OF PULMONARY HYPERTENSION

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THE importance of pulmonary hypertension in cardiac surgery has been stressed frequently in the recent literature. This has revived interest in the experimental study of this problem, including the hemodynamic effects of the hypertension and the resultant changes in the pulmonary vasculature.

To investigate the effects of pulmonary hypertension, a satisfactory experimental method of consistently producing significant elevations of the pulmonary arterial pressure must be developed. This has, in the past, been attempted in a variety of ways: by anoxia, pulmonary embolization, the production of intracardiac and extracardiac shunts in a left-to-right direction, experimental mitral stenosis, and anastomosis of a systemic artery and a pulmonary artery.

The purpose of the present study was to produce pulmonary arterial hypertension by "banding" the pulmonary veins of dogs with cellophane. The effect of a reduction in size of the pulmonary vascular bed or of an increase in the pulmonary blood flow in dogs that already had pulmonary hypertension was then undertaken and the resultant histologic changes in the pulmonary vascular tree were studied.

MATERIAL AND METHOD

Ten adult mongrel dogs weighing from 13 to 18 kg. were used. Eight of the dogs underwent preoperative cardiac catheterization, and the pressures on the right side of the heart as well as the pulmonary arterial wedge pressures were recorded by means of the strain gauge manometer with photokymographic assembly as described by Wood.[15] For these recordings the dogs were anesthetized with pentobarbital sodium (30 mg. per kilogram of body weight) given intravenously and the catheter was introduced into the heart via the right or left jugular vein.

One or two weeks later a left posterolateral thoracotomy was performed. Anesthesia was induced with pentobarbital sodium and maintained with ether given intratracheally. The thorax was entered through the fourth intercostal

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space. All the pulmonary veins draining the left lung were isolated as close to the left atrium as possible and individually wrapped with a laminated band of cellophane measuring 6 mm. in width. This band was loosely tied around each vein over a circular metal rod measuring 5 mm. in diameter, in an endeavor to

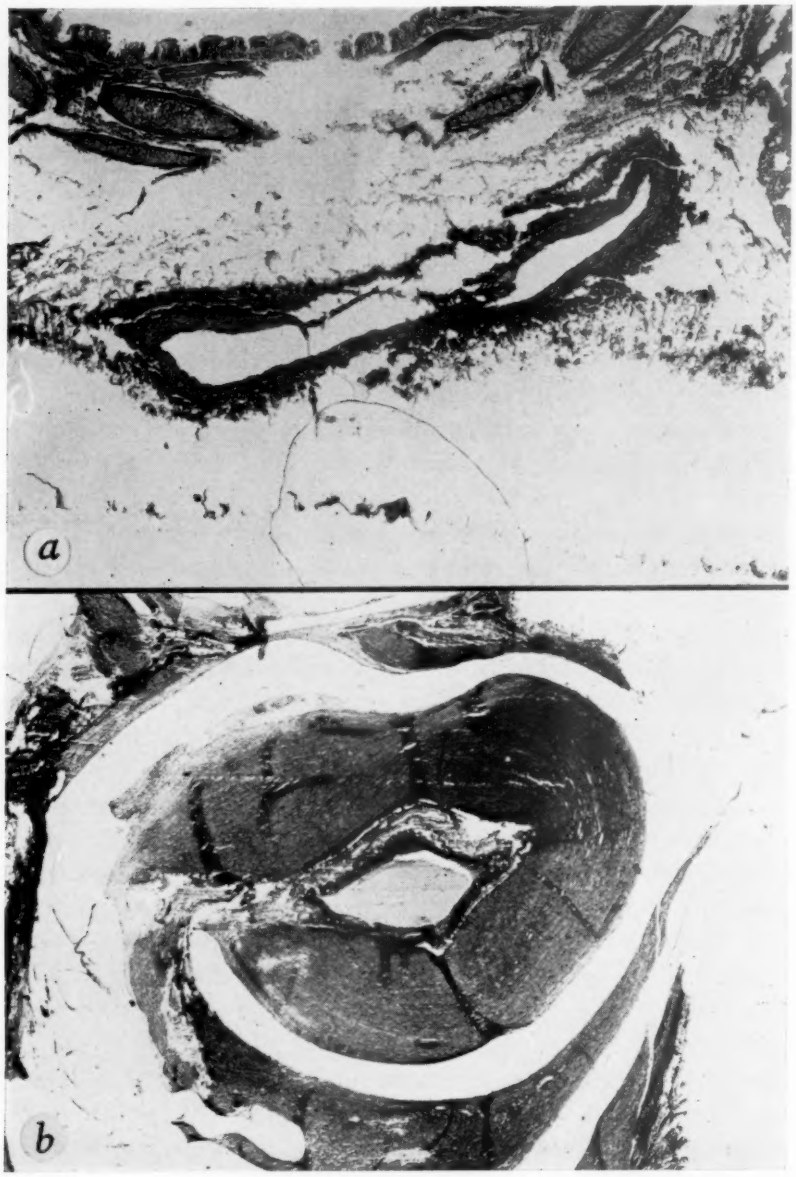

Fig. 1.—*A*, Normal pulmonary vein (Verhoeff's elastic tissue stain with van Gieson's connective tissue stain; ×20). *B*, Cellophane and reactive fibrous tissue surrounding and compressing pulmonary vein (ELVG; ×14).

avoid acute constriction of the veins. Fig. 1, *A* shows a normal pulmonary vein and Fig. 1, *B* demonstrates the marked fibrotic reaction that occurs around the vein with time in response to the cellophane and that causes pulmonary venous obstruction.

One week after the first operation a second cardiac catheterization was carried out and the same pressure measurements as those determined preoperatively were made. Two weeks after the first operation, a thoracotomy was performed on the right side and all the pulmonary veins draining the right lung were treated in a manner similar to the treatment of those draining the left lung. Subsequent cardiac catheterization studies were repeated on the 9 dogs that survived, at intervals of 2 weeks, 6 weeks, and 4 to 6 months after the second operation.

The 9 dogs that survived both operations underwent a third operation 5 to 8 months after banding of the pulmonary veins. In 7 the operation consisted of lobectomy with removal of one (2 dogs) or 2 (5 dogs) lobes of the right lung, and in 2 of the 9 dogs a side-to-side anastomosis between the aorta and the left main pulmonary artery was effected; the aorticopulmonary fistula measured 5 mm. in diameter in both dogs. Of the 9 dogs that were subjected to the third operation, 4 survived. On one of these an aorticopulmonary anastomosis was performed at the third operation. In each of 2 dogs 2 lobes had been resected, and in the remaining animal a lobectomy of one lobe had been performed. Three months later the 4 dogs that survived the third operation were catheterized and pressures were measured in the right side of the heart, in the pulmonary artery, and in the pulmonary arterial wedge position.

Sections of pulmonary tissue were obtained from each dog, either at necropsy or by biopsy at the time of the third operation. Serial sections prepared from these were stained with hematoxylin and eosin and Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain. These sections were compared with similar sections from normal dogs for evidence of changes in the pulmonary vascular tree. Representative sections from each dog were stained with potassium ferrocyanide and hydrochloric acid counterstained with basic fuchsin (Berlin blue reaction) to demonstrate the iron content and were compared with sections from normal dogs.

RESULTS

The results in the 10 dogs are summarized in Table I.

Preoperative Pressure Studies.—In the 8 dogs catheterized preoperatively, the mean pressure in the pulmonary artery varied from 13 to 18 mm. Hg and the mean pulmonary arterial wedge pressure varied from 3 to 6 mm. Hg.

Pressure Studies After Unilateral Pulmonary Venous Banding.—After banding of the left pulmonary veins, only one dog (Dog No. 6) showed an elevation of the pulmonary arterial pressure and this increase, though marked, was not associated with a corresponding rise in the pulmonary arterial wedge pressure. The explanation for this elevation of pressure is not readily apparent, but its significance is questionable since subsequent pressure recordings were normal.

Pressure Studies After Bilateral Pulmonary Venous Banding.—Once the pulmonary veins from the right lung as well as those from the left lung had been banded, several of the dogs began to show elevation in the pulmonary

TABLE I. EXPERIMENTAL PULMONARY HYPERTENSION: SUMMARY OF RESULTS*

DOG	PREOPERATIVE PRESSURE		FIRST OPERATION, PRESSURE AFTER UNILATERAL BANDING		SECOND OPERATION, PRESSURE AFTER BILATERAL BANDING						THIRD OPERATION	PRESSURE 3 MONTHS AFTER THIRD OPERATION		PULMONARY VASCULAR CHANGES (TIME AFTER THIRD OPERATION)	IRON CONTENT, GRADE
					2 WEEKS		6 WEEKS		4 TO 6 MONTHS						
	PULMONARY ARTERY	WEDGE	PULMONARY ARTERY	WEDGE	PULMONARY ARTERY	WEDGE	PULMONARY ARTERY	WEDGE	PULMONARY ARTERY	WEDGE		PULMONARY ARTERY	WEDGE		
1	–	–	–	–	37	22	(Dead after second operation)								
2	–	–	–	–	44	31	52	37	53	33	Lobectomy (RAL, RCL)	–	–	Medial hypertrophy, mild intimal proliferation (same day)	4
3	18	4	17	3	24	4	37	11	30	12	Lobectomy (RDL, RIL)	42	14	Medial hypertrophy, intimal proliferation (1 month)	2
4	16	4	19	5	19	8	21	7	18	10	Aorticopulmonary anastomosis	–	–	0 (same day)	2
5	15	6	17	5	23	8	19	8	17	4	Lobectomy (RAL, RCL)	–	–	Minimal medial hypertrophy (same day)	3
6	17	5	38	7	16	3	–	–	17	7	Aorticopulmonary anastomosis	25	17	Medial hypertrophy, intimal proliferation (6 weeks)	2
7	14	3	16	3	16	4	28	14	31	20	Lobectomy (RAL)	31	19	Medial hypertrophy (6 weeks)	3
8	13	3	15	6	17	8	25	14	16	–	Lobectomy (RAL)	–	–	Medial hypertrophy (1 day)	1
9	17	4	18	4	20	6	–	–	22	–	Lobectomy (RAL, RCL)	26	6	Minimal media hypertrophy (2 months)	1
10	18	–	25	5	34	25	–	–	32	24	Lobectomy (RCL, RDL)	–	–	Medial hypertrophy, mild intimal proliferation (2 days)	2

*Pulmonary artery and pulmonary wedge pressures are expressed as mean values in millimeters of mercury.

pressures. On an arbitrary basis it was decided that an increase in the mean pulmonary arterial pressure of less than 10 mm. Hg above the preoperative value would be considered not significant, an increase of 10 to 19 mm. would signify mild pulmonary hypertension, an increase of 20 to 29 mm. would signify moderate hypertension, and an increase of more than 29 mm. would signify pulmonary hypertension. Two dogs (Dogs No. 1 and 2) had not been catheterized preoperatively; hence a value of 16 mm. Hg, the average of the preoperative pulmonary arterial mean pressure in the other 8 dogs, was assumed as the preoperative mean pulmonary arterial pressure for these 2 dogs.

Two weeks after bilateral banding of the pulmonary veins, 3 dogs (Dogs No. 1, 2, and 10) showed elevations in their pulmonary arterial pressures, one of mild and 2 of moderate degree. In each of these 3 cases the pulmonary wedge pressure was also elevated. One of the latter dogs (Dog No. 1) died of severe pulmonary edema 2 weeks after bilateral venous banding had been accomplished. Four weeks later the pulmonary arterial pressure and the pulmonary wedge pressure had increased in 3 additional dogs, mildly in 2 (Dogs No. 7 and 8) and moderately in one (Dog No. 3).

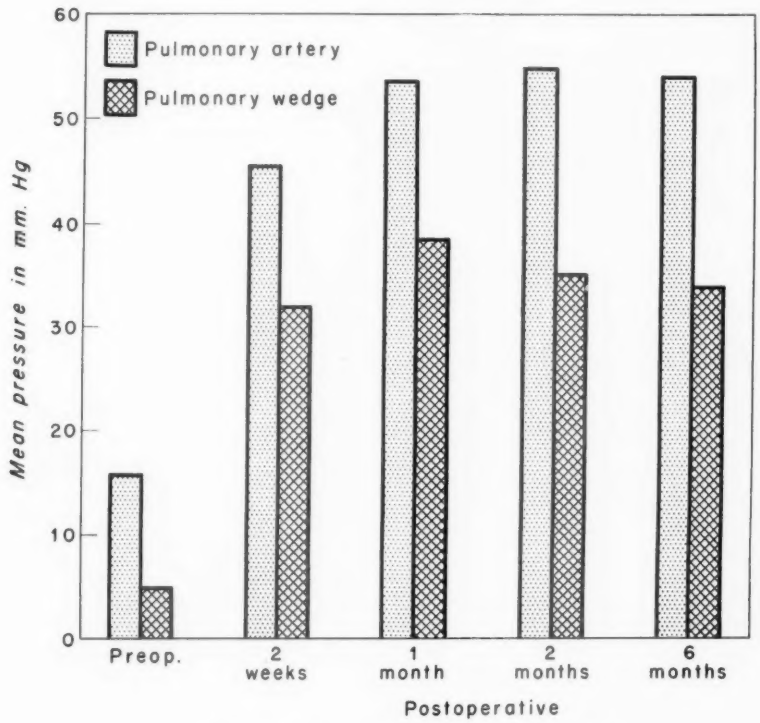

Fig. 2.—Pressure pattern in Dog No. 2.

Cardiac catheterization done from 4 to 6 months after bilateral pulmonary venous obstruction had been accomplished revealed no significant changes in general from the findings obtained in the studies done 6 weeks after the second operation. In one dog (Dog No. 8) the pulmonary pressure became slightly elevated 6 weeks after the second operation but 4 months later it had returned to normal. Fig. 2 illustrates the pattern in Dog No. 2, which was characteristic

of all the dogs in which there was significant elevation of the pulmonary pressure. The dogs that had not shown an increase in pressure 6 weeks after the second operation did not experience a change subsequently.

Pressure Studies After Pulmonary Resection.—It will be recalled that in 7 dogs the third operation was done 4 to 6 months after bilateral pulmonary venous banding had been accomplished. Four animals failed to survive the latter procedure for any significant time. They died of severe pulmonary edema within a few to 48 hours after pulmonary resection.

Each of the 3 dogs that survived pulmonary resection was studied by cardiac catheterization 3 months after the last operation. In 2 instances no further increase in pressures was recorded (Dog No. 7, one lobe resected; Dog No. 9, 2 lobes resected). In the one remaining dog of those on which pulmonary resection had been performed (Dog No. 3, 2 lobes resected), the mean pulmonary arterial pressure had increased to 42 mm. Hg from 30 mm. Hg that existed shortly before resection of pulmonary tissue. No essential change in the pulmonary arterial wedge pressure was observed.

Pressure Studies After Aorticopulmonary Anastomosis.—Of the 2 dogs that had an aorticopulmonary anastomosis, one died of pulmonary edema several hours after operation. The single survivor (Dog No. 6) 3 months later showed a rise of only 8 mm. Hg in mean pulmonary arterial pressure.

Histologic Changes.—Serial sections of the lung were made and examined in 9 of the 10 dogs. These were procured at necropsy or by biopsy 6 to 9 months after all the pulmonary veins had been banded and were compared with serial sections of lung from normal dogs. Fig. 3, *A* illustrates a normal small muscular artery and Fig. 3, *B* a normal pulmonary arteriole. Eight of the 9 dogs exhibited pulmonary vascular changes of mild-to-moderate degree. These changes were found mainly in the small muscular arteries, the arterioles, and the small veins of the lung. The most consistent finding was that of medial hypertrophy, and this was the first and often the only evidence that a histologic change had occurred in the small pulmonary vessels. The medial thickening, sometimes concentric and sometimes eccentric, was due to hypertrophy of the smooth muscle in the media and resulted in narrowing of the lumen (Fig. 4). Intimal proliferation, seen less frequently, was found in only 4 of the 8 dogs in which pulmonary changes were demonstrated (Fig. 5). Fibrous thickening of the intima, usually in an eccentric fashion, appeared to represent a more advanced stage of pulmonary vascular change, since it was seen only in those dogs that exhibited the greatest degree of medial hypertrophy. It was usually associated with splitting of the internal elastic lamina and it further constricted the lumen of the small muscular artery or the arteriole. This change was not seen in the small pulmonary veins. In the present study, intimal proliferation had not advanced to the stage of complete occlusion of any of the small pulmonary vessels, nor was necrotizing arteritis observed. In general, the incidence and the severity of the histologic changes in the pulmonary vascular tree were directly related to the degree of induced pulmonary hypertension.

An attempt was made to quantitate the degree of medial hypertrophy and intimal proliferation. This was unsuccessful because of the wide variation in the thickness of the media and the intima found in normal dogs.

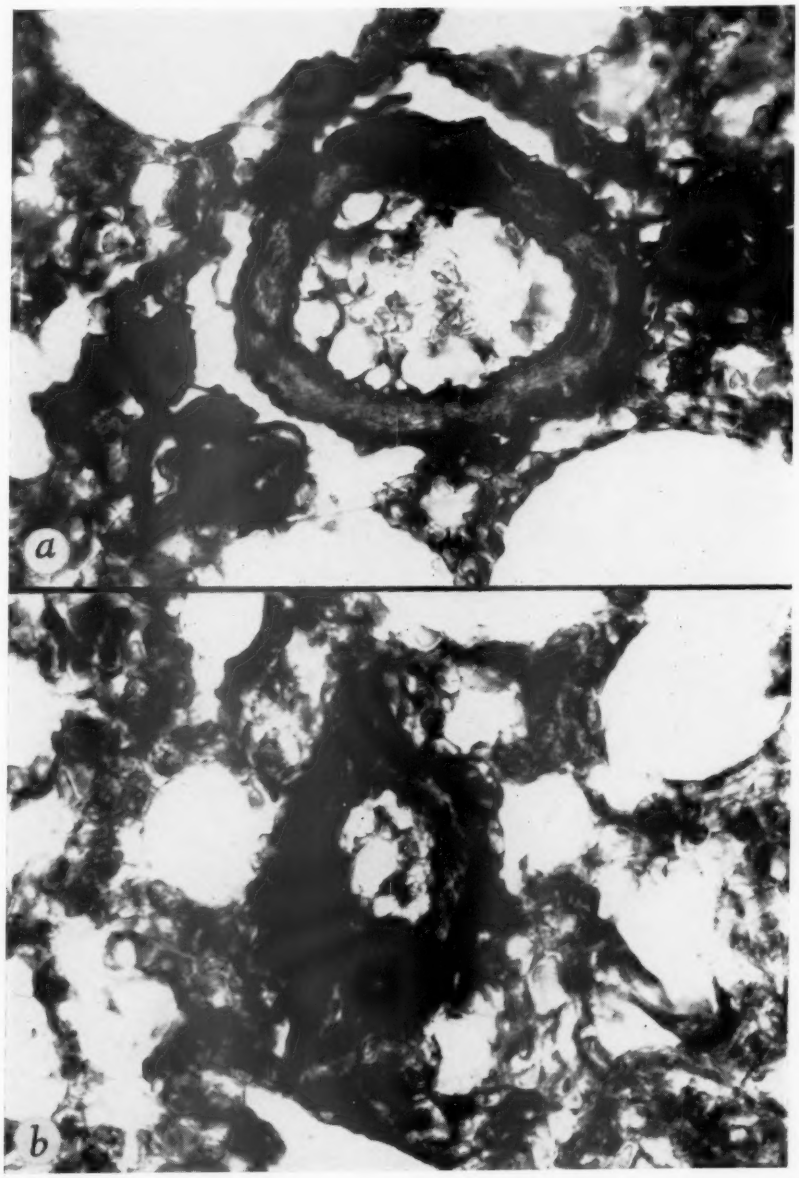

Fig. 3.—Controls. *A*, Normal small muscular artery of the lung (ELVG; ×530). *B*, Normal pulmonary arteriole (ELVG; ×780).

Representative sections from the lung of each dog were stained for iron content and compared with normals. The hemosiderin was deposited in macrophages which, for the most part, were collected into focal aggregations in and around several alveoli. Graded on the basis of 0 to 4, none of the normals used for comparison attained a grade of higher than 1. In 7 of 9 cases the

amount of iron deposited in the lung was increased over that in controls. As shown in Table I, in 3 animals the deposits were of such proportions as to be graded 3 in 2 instances and 4 in one.

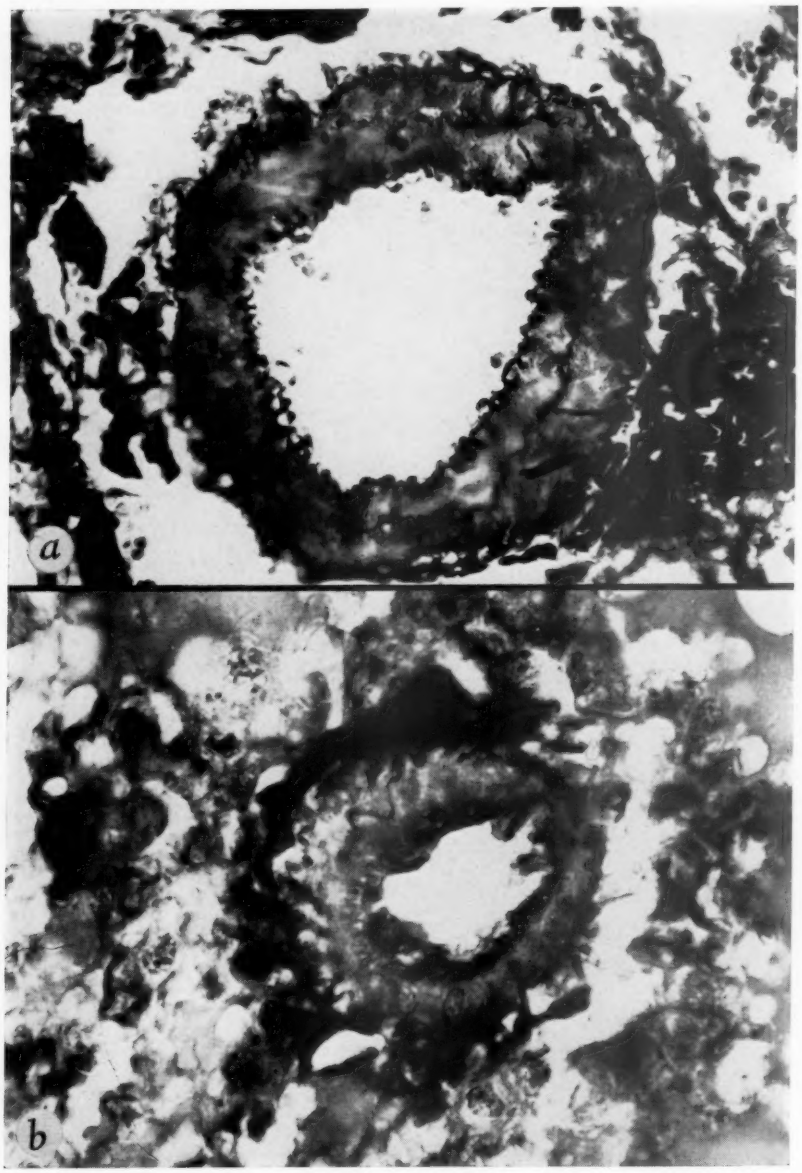

Fig. 4.—*A*, Small muscular artery with medial thickening (Dog No. 8) (ELVG; ×400). *B*, Pulmonary arteriole with medial hypertrophy (Dog No. 2) (ELVG; ×780).

COMMENT

The present study deals with one method of experimentally producing pulmonary hypertension, namely, by interfering with the pulmonary venous return. Clinical support for this method is gained from the reports of Edwards

and Burchell[6] and Emslie-Smith and co-workers.[7] Van Bogaert and co-workers[12] ligated one or more of the pulmonary veins in dogs and observed a two-fold rise in the pulmonary arterial pressure. The use of cellophane to stimulate fibrosis and gradual occlusion of a blood vessel has been demonstrated by

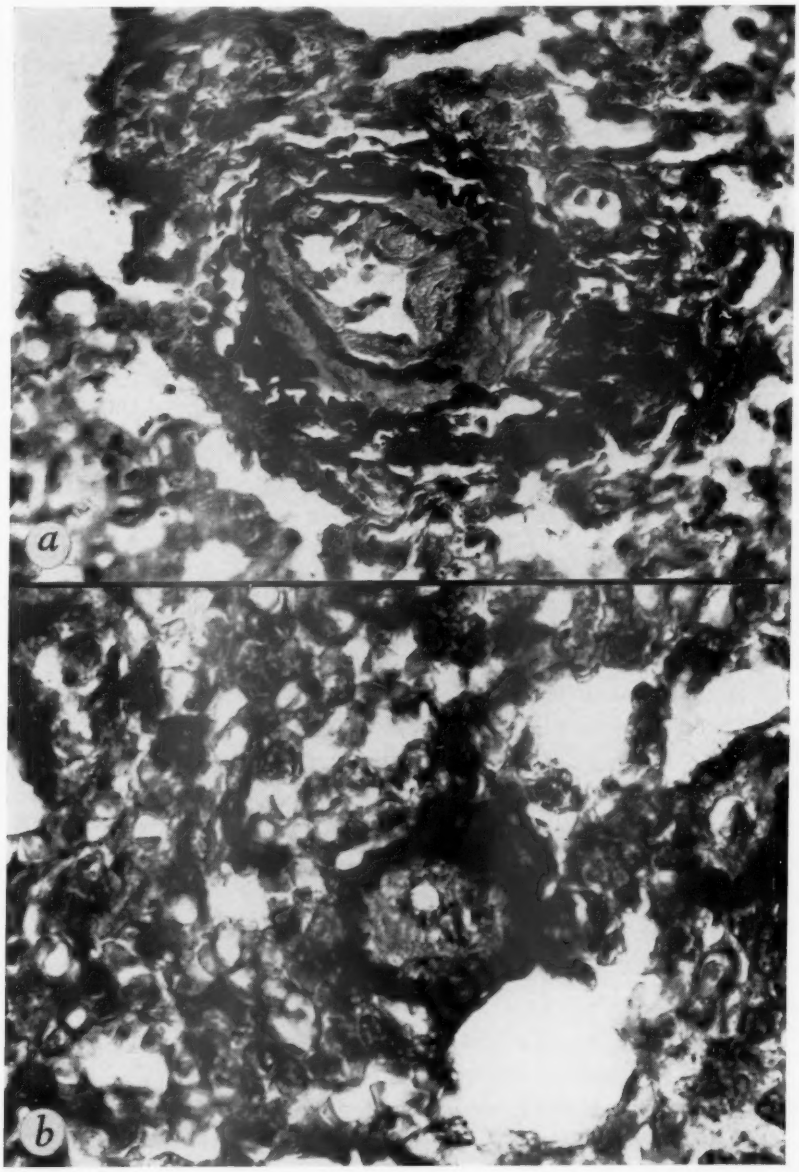

Fig. 5.—*A*, Small muscular artery showing focal atrophy of the media with irregular intimal proliferation (Dog No. 6) (ELVG; ×400). *B*, Pulmonary arteriole almost occluded by intimal proliferation (Dog No. 10) (ELVG; ×780).

Boucek, Grindlay, and Burchell[1] and by Donald and Kirklin,[5] among others. Boucek and his associates,[1] after wrapping the pulmonary veins with cellophane, demonstrated pulmonary vascular changes in one dog 2 years later. Ferguson, Berkas, and Varco[8] wrapped cellophane around the pulmonary

veins in 13 dogs, 9 of which died of pulmonary edema within 2 weeks. The 4 survivors had minimal elevation of the pulmonary arterial pressure but developed medial hypertrophy of the veins and arterioles in 2 to 4 months. This method was selected in the present study in the hope that the progressive yet gradual obstruction to the pulmonary venous return created by the reaction around the cellophane would enable the dog to tolerate higher pulmonary pressures than would otherwise be possible. Fig. 1, *B* illustrates the marked reaction that occurs around the pulmonary vein but, despite this, the pulmonary arterial pressure, after a preliminary rise, leveled off and showed little or no subsequent change over a 3-month period.

The absence of an appreciable rise in pulmonary arterial pressure in some dogs is probably best explained by the work of Wearn and his associates.[13, 14] They demonstrated that an increased volume of blood could be accepted by the lung through the opening up of additional capillary channels and by means of capillary distention. There must, however, be a rather abrupt limit to this method of adaptation on the part of the lung if one is to explain the rapidly fatal pulmonary edema that developed in 4 of the 7 dogs in which lobectomy was performed. Of the 3 dogs that survived lobectomy, only one showed a significant rise in the pulmonary arterial pressure. This group is too small to permit any conclusions. Cournand[3] has shown in man that the resting pressure in the pulmonary artery is unaltered after pneumonectomy, but whether this would also be true in the presence of increased pulmonary vascular resistance in the remaining lung is not known.

The pulmonary vascular lesions were not severe. This is perhaps explained by the facts that the pulmonary hypertension in these animals was not very marked even in animals with greatest elevations and the lungs were examined histologically only 6 to 9 months after the pulmonary veins had been banded. The lesions produced by Ferguson and his associates[9] and by Dammann, Baker, and Muller[4] after anastomosis of a systemic and a pulmonary artery appeared within 2 weeks and were severe after several months. In their experiments a high-pressure pulsatile flow of fully oxygenated blood entered the pulmonary circuit. Such was not the case in the experiments herein reported except in one surviving dog.

Some investigators[8, 11] have indicated that puppies are more suitable for these experiments than adult dogs. This premise is based upon the work done in man by Civin and Edwards[2] who showed that the fetal characteristics of pulmonary arteries, that is, the thickened media and narrowed lumen, persist for several months after birth.

Lendrum, Scott, and Park[10] have reported focal accumulations of hemosiderin in the lungs of patients who have mitral stenosis. This was observed in most of the dogs in the present study but was well marked in only 3.

At present there is no completely satisfactory method by which consistent elevations of rather marked degree of the pulmonary arterial pressure may be achieved. Perhaps if cellophane bands were placed around the pulmonary veins of very young dogs and these were observed for several years, a higher

level of pulmonary hypertension might result. However, the present experiments have served to emphasize the fact that in the dog a fine dividing line exists between the amount of pulmonary venous obstruction which has no measurable effect upon the pulmonary arterial pressure on the one hand and the amount that produces fatal pulmonary edema on the other.

SUMMARY

A method for the experimental production of pulmonary hypertension consisting of "banding" the pulmonary veins with cellophane is described. Some rise in pulmonary arterial and pulmonary arterial wedge pressures was observed in 5 of 9 dogs 6 months after banding. The added effect of pulmonary resection and of aorticopulmonary anastomosis was also studied. The small pulmonary vessels showed changes consisting mainly of medial hypertrophy with occasional intimal proliferation in 8 of the 9 dogs.

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AN EFFICIENT BLOOD HEAT EXCHANGER FOR USE WITH EXTRACORPOREAL CIRCULATION

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GOLLAN[4-8] and others[1, 9] have shown in the experimental animal that body temperature may be lowered or restored by cooling or warming the inflowing oxygenated blood during extracorporeal circulation. At the Duke Hospital, we have preferred to use a combination of hypothermia and extracorporeal circulation (with or without cardioplegia) in all open heart operations, for reasons described elsewhere.[10]

Originally, we achieved hypothermia by the usual means of ice packs or the refrigerated blanket applied after the induction of anesthesia. These methods have certain disadvantages such as prolonged anesthesia time for cooling, poor control of hypothermia due to downward temperature drift after removal of the coolant, and slow and prolonged rewarming.

In order to attain hypothermia of a desirable level (30° to 32° C.) within the few minutes just prior to the cardiac portion of the operative procedure and to restore body temperature to near normal immediately thereafter, we have developed a simple blood heat exchanger suitable for use with any type of heart-lung machine. The device is inserted in the arterial inflow line between the heart-lung machine and the patient's cannulated artery.

The heat exchanger is specifically designed to exchange heat between water and a liquid having the physical characteristics of blood. Particular attention was given to providing a device which would be capable of thorough cleaning and inspection, free of bubble-trapping crevices or surfaces, simple to assemble, and safe from intrusion of water or other foreign matter into the blood stream.

DESCRIPTION

The heat exchanger (Fig. 1) is made of type 304 stainless steel throughout without the use of any other alloy as a brazing or soldering agent. It consists of an outer cylindrical jacket 15¼ inches long and 2¼ inches in diameter through which 24 straight thin-wall (0.035 inch) tubes 0.180 inch in inside diameter run longitudinally. The ends of the tubes are welded into a header plate (Fig. 2, *A*) at each end and the surfaces in contact with blood are highly polished. Each end of the exchanger cylinder is threaded to take a stainless

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steel cap (Fig. 2, *B*) fashioned with a beaded tube to which the usual plastic blood inflow and outflow tubing is attached. The interior of each cap is conically shaped, providing sloping surfaces for the flowing blood at each end of

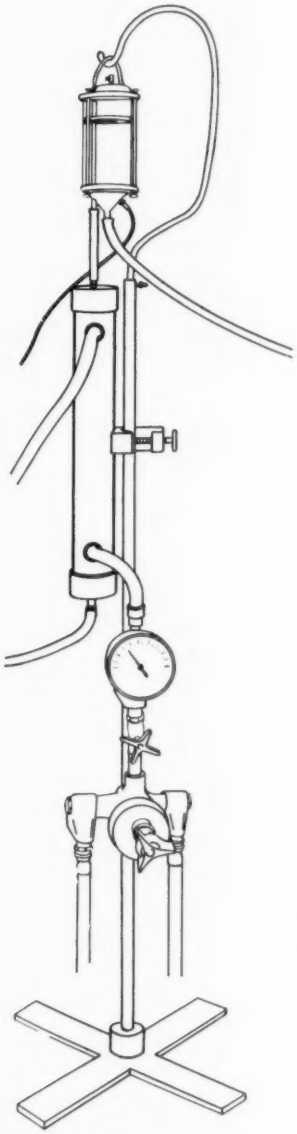

Fig. 1.

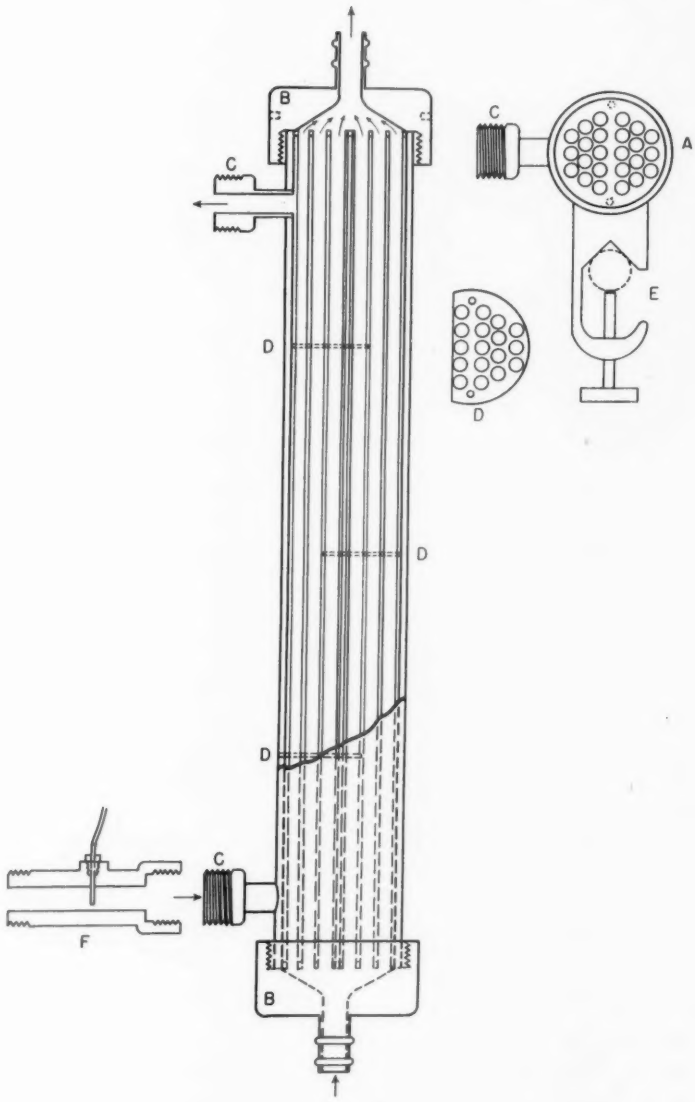

Fig. 2.

Fig. 1.—Sketch showing complete heat exchanger assembly. The tube entering the bottom of the exchanger from the left carries oxygenated blood from the heart-lung machine. The tube leading to the right from the bottom of the bubble trap above carries the temperature-regulated inflowing blood to the patient's artery. The detachable thermistor lead is shown leading to the left from the bottom of the bubble trap. The automatic thermoregulated water mixing valve with its attached hot and cold water supply hoses is shown mounted on the floor stand just below the exchanger. The water discharge is shown leading to the left near the upper end of the exchanger.

Fig. 2.—Schematic cutaway sketch of blood heat exchanger. See text for description.

the exchanger to avoid the trapping of any gas bubbles. The caps, when tightened against thin Teflon gaskets, completely seal the exchanger for use. Near the bottom of the exchanger jacket is a water inlet with ¾-inch hose bib fitting

(Fig. 2, *C*) through which cold or warm water enters the exchanger jacket and flows upward to a similar outlet at the top of the exchanger. The top outlet also has a hose bib fitting to allow the waste water to be carried to a sink or drain by an ordinary garden hose.

Baffle plates (Fig. 2, *D*) within the jacket of the exchanger insure thorough circulation of the cooling or warming water around the thin tubes carrying the blood.

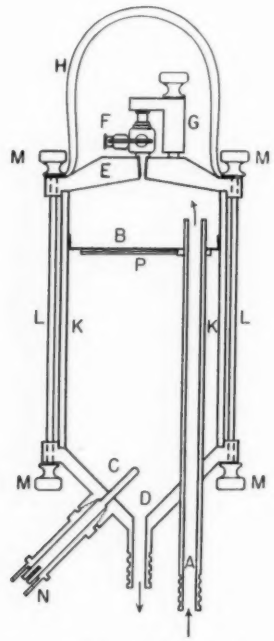

Fig. 3.—Schematic cross-sectional sketch of bubble trap used with heat exchanger. The fine mesh stainless steel disc (*B*) is shown supported on the struts (*P*). The 2 Tygon plastic gaskets sealing the glass cylinder (*K*) against the stainless steel top and bottom are not shown.

The heat exchanger is mounted in a vertical position (Fig. 1) on a heavy floor-type ring stand by means of a slotted mount (Fig. 2, *E*) and tightening screw attached to the exchanger jacket. The stand pole (Fig. 1) is bored out at the top for insertion of a steel loop holder from which is suspended a specially constructed bubble trap shown in detail in Fig. 3. After the blood leaves the heat exchanger it enters the bubble trap through a stainless steel tube leading to the top of the trap (Fig. 3, *A*). This inflow tube passes through a tight-fitting disc (Fig. 3, *B*) of fine mesh stainless steel screen (100 by 90 wire size 0.0045 inch) placed approximately 1 inch from the top of the trap. This screen disc, pressed with $\frac{3}{16}$-inch turned-up edge which fits snugly against the trap's circular glass wall, is supported by 2 small rod struts (Fig. 3, *P*) $\frac{1}{16}$ by 2 inches attached to a narrow ring on the inflow tube (Fig. 3, *A*). In the side of the conical bottom is mounted a stainless steel thermistor tip (Fig. 3, *C*) with a detachable coupling (Fig. 3, *N*) for wire leads on the outside of the trap (Fig. 2). This mounted portion of the thermistor is screwed in over an O ring seal and is capable of steam sterilization. The stainless steel conical bottom (Fig. 3, *D*) with inflow tube, thermistor seat, and outflow tube is made up as one piece so as to facilitate cleaning and assembly. The top of the trap (Fig. 3, *E*), also slightly

conical, contains a tapered hole at its apex to take the male end of a disassembleable 3-way stopcock.* The stopcock (Fig. 3, *F*), which is removable for cleaning, is locked in place during use by a locking bar (Fig. 3, *G*). Blood samples or any accidentally accumulated gas may be removed from the trap when desired through this stopcock vent. A heavy ring attached to the top of the bubble trap (Fig. 3, *H*) permits its suspension from the stand holder (Fig. 1).

The side walls of the bubble trap (Fig. 3, *K*) consist of a 3-inch length of Pyrex glass tubing 2¾ inches in outside diameter, wall thickness 3/16 inch. The stainless steel top and bottom seal against this Pyrex glass tube with 3/16 inch washers of flat Tygon plastic† 1/16 inch in thickness. The seal is accomplished by the vertical rods and thumb screws (Fig. 3, *L* and *M*). The assembled bubble trap with attached plastic tubing connecting it to the heat exchanger is autoclaved in the steam sterilizer as one unit. The bubble trap has a capacity of 300 c.c. and the heat exchanger a capacity of 175 c.c. Once the exchanger is attached to the floor stand, the water intake is connected by a short length of garden hose to an automatic thermoregulated water mixing valve (Fig. 1). The effluent water temperature is regulated by a hand valve and recorded by a dial thermometer. Once the effluent water temperature is set, the automatic thermoregulator mixing valves hold the temperature to within ±0.5° C. of this setting regardless of changes in pressure or temperature in the hot and cold water supply lines. Should it be desirable to monitor the water temperature on the same instrument used for recording the blood and body temperatures, a detachable thermistor lead with screw base may be mounted in a nipple (Fig. 2, *F*) and attached to the water inlet of the exchanger. The heat exchanger assembly on its floor stand consumes very little room and is usually placed near the operating table between the heart-lung machine and the patient. The hot and cold tap water are brought to the mixing valve by conventional rubber garden hoses. The thermistor leads from the bubble trap (inflow blood temperature), esophagus, rectum, inflow water, and so forth are plugged into a commercially available multiple channel thermistor-thermometer.‡

DISCUSSION

The heat transfer characteristics of the exchanger at various blood and water flow rates are illustrated by Fig. 4. The efficiency of the heat exchanger during extracorporeal circulation is illustrated by the temperature chart (Fig. 5) from a patient undergoing open heart surgery for correction of a third recurrence of mitral stenosis. In this patient, the arterial inflow was via the femoral artery. Before commencing the intracardiac procedure, perfusion was started without caval occlusion, employing only the outflow from the femoral vein. The patient's initial esophageal temperature of 36.5° C. was reduced to 31° C. in the 7 minutes required for cannulation of the superior vena cava and final preparation for opening the heart. During the next 10 minutes required for the open heart procedure, the esophageal temperature was maintained be-

*Becton-Dickson Company, Rutherford, N. J.

†Cut from press polished Tygon sheet plastic formulation S-22-1. U. S. Stoneware Company, Akron 9, Ohio.

‡Yellow Springs Instrument Company, Yellow Springs, Ohio.

tween 29.5° and 30° C. When the heart was closed, rewarming was begun while continuing the perfusion via the femoral vessels only. Within 7 minutes

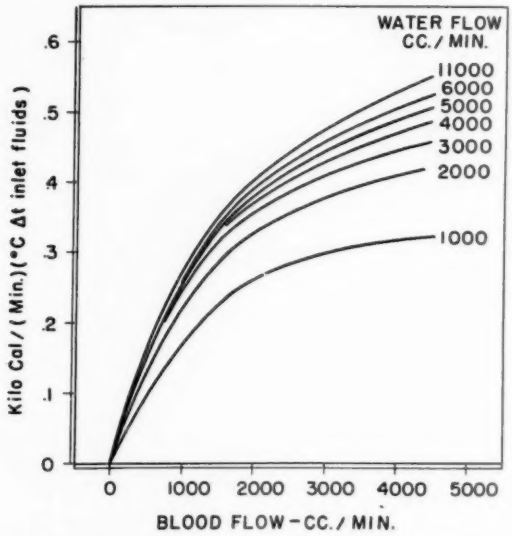

Fig. 4.—The heat transfer characteristics of the blood heat exchanger at varying flow rates of blood and water. The original data for this graph were obtained with water flowing in both the blood and water jacket channels. These data were then recalculated for blood flowing through the exchanger on the basis of Colburn's[3] analysis of forced convection heat transfer employing the values for the physical properties of blood.

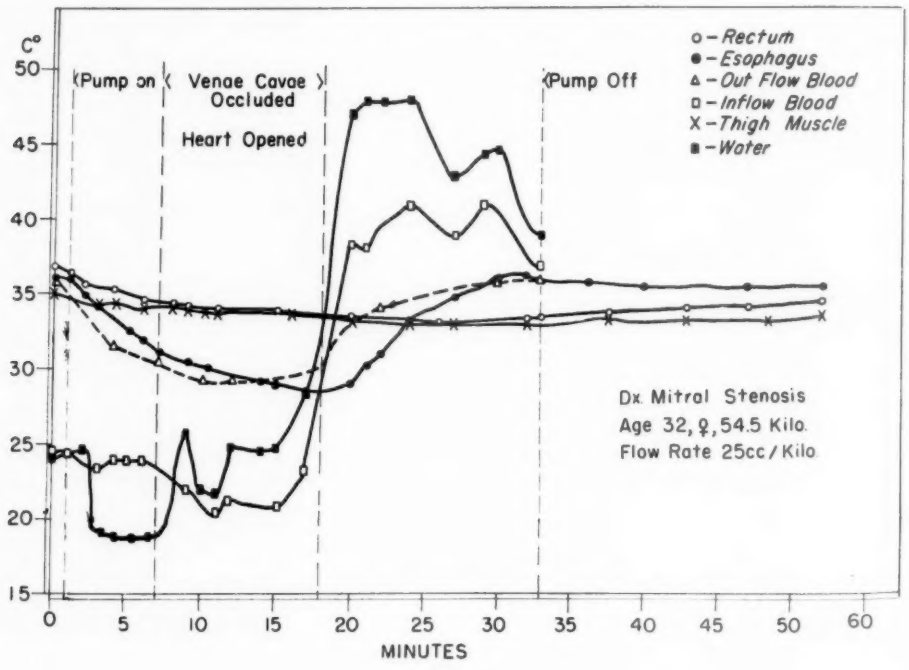

Fig. 5.

the esophageal temperature had returned to 35° C. On the basis of experiments to be described elsewhere,[2] we have found that the mid-esophageal temperature most closely reflects the vital organ temperatures.

Because of the possibility of bubbles being released from oxygen-saturated plasma during the rewarming of the blood in the exchanger, we have included the specially designed bubble trap (Fig. 3) just distal to the exchanger.

The essential feature of this bubble trap is a fine mesh stainless steel disc through which the blood must pass in its downward course to the bottom outlet. The swirling motion of the blood in the top of the trap caused by the inflow jet does not extend below the mesh disc. Thus the trap mesh serves 3 purposes: (1) It prevents swirl entrainment of small bubbles downward to the conical outlet. (2) It retains above it, by virtue of surface tension, bubbles which might enter the trap through the inflow tube. (3) It acts as a final filter for fibrin and clots.

While we have employed the heat exchanger with extracorporeal circulation for producing hypothermia and rewarming, this device, because of its application to any type of heart-lung or artificial kidney circuit, is equally useful in maintaining normal body temperature during extracorporeal circulation when hypothermia is considered undesirable.

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ADDENDUM

Since the submission of this manuscript, the exchanger end caps (Fig. 2, *B*) have been modified so as to clamp on rather than screw on as shown. Also, a larger volume U flow exchanger of similar design has been employed with larger patients. This latter exchanger permits a smaller gradient between blood inflow temperature desired and the inflow water temperature at high blood flow rates.

HEMODYNAMIC MECHANISMS WHICH AUTOMATICALLY MAINTAIN A RELATIVELY CONSTANT BLOOD VOLUME DURING CARDIOPULMONARY BYPASS

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A SIMPLE reliable method of measuring the patient's blood volume, immediately and quantitatively, might greatly increase the safety of whole body perfusion. Sudden alterations in blood volume may cause severe circulatory disturbances during open heart operations and corrective measures may be ineffective, or even inappropriate, because the excess or deficit in blood volume cannot be quickly and accurately determined. It has become increasingly evident that maintenance of a relatively constant blood volume is one of the most important factors in carrying out a perfusion characterized by few, if any, deviations from normal physiologic function, as reflected by the parameters usually monitored (pressures, blood gases, and pH) and by prompt complete recovery of the patient.

Since there is no direct method at present for detecting changes in blood volume instantly and accurately, this problem has been approached by using indirect methods, such as attempts to control flow rates precisely, measurements of blood loss, and measurements of the volume of the extracorporeal circuit. Preset, precalibrated arterial and venous pumps have been widely employed in attempting to achieve identical flow rates to and from the patient, but an entirely satisfactory venous pump probably requires the incorporation of certain critical characteristics which have not been clarified.

Gravity drainage of the venous blood returning to the cavae eliminates problems associated with the use of a venous pump, and this method is gaining widespread acceptance. The gravity method, combined with slight negative pressure, has been used successfully by Kirklin and his associates,[3] who have also employed electronic leveling devices which automatically permit the venous outflow through the caval catheters to control the perfusion rate and equalize the flow to and from the oxygenator. "The rate of return of oxygenated blood from the apparatus to the patient is governed by, and is at all times equal to, the rate of outflow of venous blood from the patient to the apparatus."[2] This is undoubtedly a splendid control system, though not an inexpensive one, and it has been reliable in a large clinical series. It should be noted that this method is based upon automatic maintenance of a constant

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volume *in the extracorporeal circuit,* however, rather than in the patient. Recognition of alterations in the blood volume of the patient is still dependent upon careful measurement of blood loss by operating room personnel and replacement of blood to restore the patient's blood volume is based entirely upon these measurements, some of which are admittedly estimates (for instance, wound drapes).

In studying hemodynamic patterns associated with total cardiac bypass, we have noted that certain basic mechanisms interact in such a way as to provide simple automatic control of the blood volume of the patient rather than of the extracorporeal circuit. Electronic devices are not needed to bring about the alterations which keep the patient's blood volume constant. The experimental observations underlying this concept have appeared helpful to us during whole body perfusion for open heart surgery and are presented because it seems likely that others may wish to employ the underlying principles.

METHODS

Equipment and techniques were standardized insofar as possible and, except for variations pertinent to each experiment, will be described only once.

1. A commercially available modification of the Gibbon-type vertical screen oxygenator* was used in all the experiments. The construction and operation of this apparatus have now become quite well standardized and no significant changes were made except for a few specific details mentioned in individual experiments.

2. Donor blood was collected from the femoral artery of other dogs. The blood bottles† were siliconized and contained 20 mg. of heparin. No attempt was made to group or cross-match the blood.

3. Mongrel dogs weighing from 12 to 45 Kg. were used in the experiments. A preliminary observation period and other measures used for long-term survival animals were not employed.

4. A right thoracotomy was performed through the fifth or sixth intercostal space. The caval cannulae were inserted through the same or through separate incisions in the right atrial appendage. The arterial cannula was inserted through a subclavian or femoral artery. Heparin (2 mg. per kilogram) was given intravenously just before the cannulae were inserted.

5. The arterial blood pressure was measured with a mercury manometer connected to a femoral artery cannula inserted into the abdominal aorta. The pressures were noted visually and recorded on the protocol sheet. Central venous pressure was measured in the inferior or superior vena cava or both with saline-filled U tubes connected to cannulae inserted into the jugular or femoral vein.

*The G-K pump-oxygenator manufactured by The Mark Company, Randolph, Mass.

†Generously supplied by the Abbott Laboratories, North Chicago, Ill., and the Baxter Laboratories, Morton Grove, Ill.

6. Oxygen (100 per cent) was administered through a cuffed endotracheal tube with a standard intermittent positive pressure respirator when the chest was open. Artificial respiration was discontinued during cardiac bypass, and the lungs were permitted to collapse.

EXPERIMENTS

Experiment 1. Relationship Between Venous Pressure, Resistance in the Caval Drainage System, Height of the Right Atrium Above the Venous Reservoir, and Arterial Perfusion Rate.—

Procedure: A mobile venous reservoir, which could be moved up and down easily, was used instead of the usual fixed reservoir on the pump table, and pressures in the superior and inferior venae cavae were recorded at various reservoir levels. The level of the venous reservoir was first placed at the same height as the right atrium and the venous pressure was noted at a perfusion rate of 100 c.c. per kilogram per minute. The venous reservoir was then lowered in progressive 10 cm. decrements and the venous pressure was recorded at each level. This procedure was carried out in 4 dogs, employing a number of different flow rates for each. The internal diameter of the caval cannulae was $\frac{3}{16}$ inch in 2 instances and $\frac{5}{16}$ inch in the other 2.

Results: The venous pressure at the varying reservoir levels and perfusion rates is shown graphically in Fig. 1 for 2 of the animals. These 2 dogs weighed about the same (15 and 16 Kg.); the smaller caval cannulae were used in one and the larger cannulae in the other. It is readily apparent that the slopes of the curves were essentially the same in all instances and there was a shift of the curve to the right with higher perfusion rates. The curves became horizontal when further lowering of the venous reservoir did not cause a further decrease in venous pressure, and these minimal levels were slightly higher at higher perfusion rates.

It seems evident that, since all of the curves had the same characteristics and were parallel, the venous pressure levels obtained on the downward slope were primarily dependent upon the pressure-flow resistance characteristics of the caval outflow tubing and connectors. The venous pressure was higher at a given perfusion rate when the smaller caval catheters were used because a greater pressure gradient was required to overcome the greater resistance of the smaller tubing.

The superior caval pressure was almost invariably lower than that of the inferior cava, the difference sometimes being as great as 20 cm. H_2O. This may be regarded as an argument in favor of recording inferior caval pressure routinely in patients. However, the occasional failure to detect excessively high superior caval pressure, caused by occlusion at some point, if only inferior caval pressure were monitored routinely, would be potentially much more serious than if the reverse were true, because of the greater vulnerability of the brain. This may more than offset the apparent advantages of observing the inferior caval pressure if only one is monitored.

Experiment 2. Relationship Between Blood Volume and Perfusion Rate When the Venous Pressure Was Maintained Between 0 and 10 cm. H_2O.—

Procedure: Six animals were used in this experiment. In each instance the caval catheters were made sufficiently large, and the height of the right atrium above the venous reservoir was made sufficiently great to insure that the venous pressure would remain low (below 10 cm. H_2O) when the perfusion

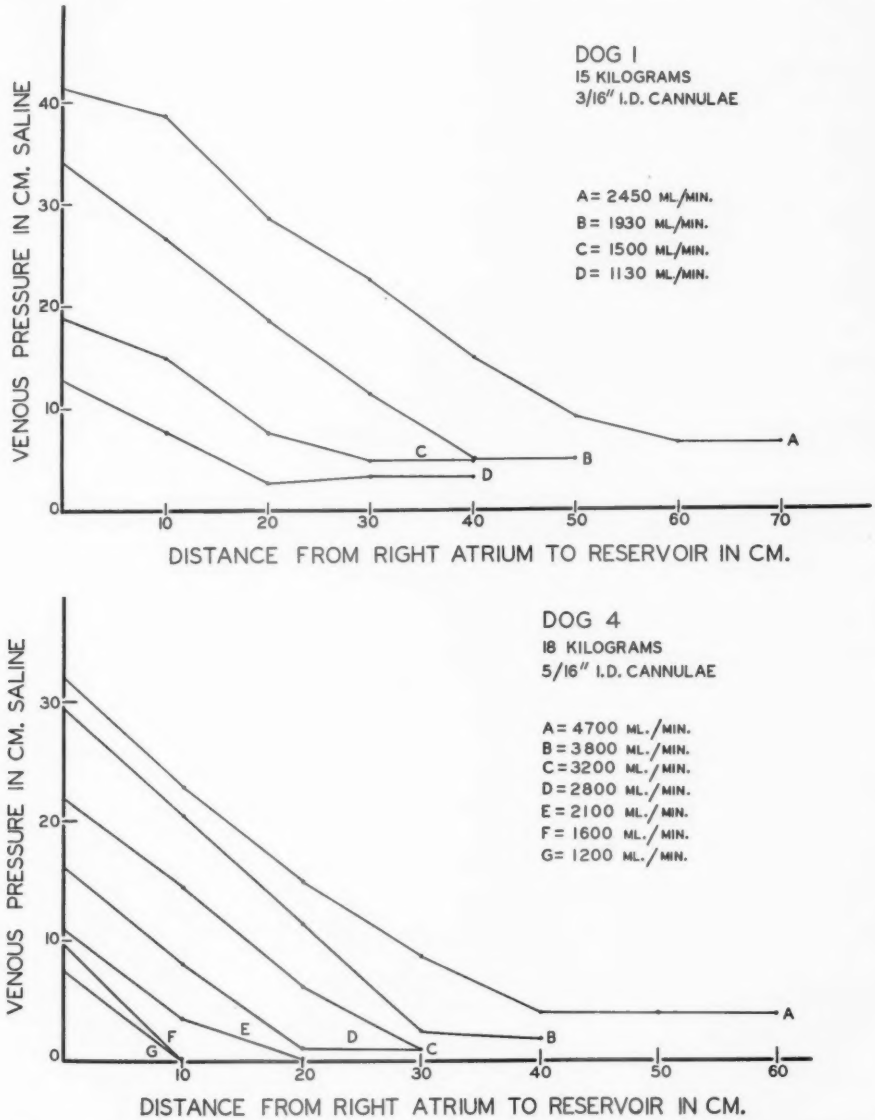

Fig. 1.—This shows the decrease in venous pressure as the venous reservoir was lowered. The slopes of the curves were the same at varying flow rates. (See text for further comment.)

rate was carried up to 150 c.c. per kilogram per minute. The oxygenator case was carefully calibrated so that any blood level could be easily read in cubic centimeters of blood. In the first dog the arterial pump was set to deliver 40 c.c. per kilogram per minute and within a short time the blood level in the

oxygenator case became stabilized. The perfusion rate was then increased to 60 c.c. per kilogram per minute and this was accompanied by a lowering of the blood level in the oxygenator case, indicating that a larger volume of blood was now in the animal. The new level became stable within one minute. The same procedure was repeated with progressive increase in perfusion rate to 80, 100, and 120 c.c. per kilogram per minute. The blood level in the oxygenator case at each rate was noted when it became stable, and the amount of blood which left the oxygenator case and entered the animal was calculated and expressed as cubic centimeters per kilogram of body weight. The perfusion rate was then progressively reduced by 20 c.c. per kilogram per minute with similar recordings being made of the blood level when it became stabilized at each new perfusion rate and this was continued until the initial rate of 40 c.c. per kilogram per minute was reached. The same procedure was carried out in the other animals, in most of which the range of perfusion rates was from 20 to 140 c.c. per kilogram per minute.

Results: The changes in blood volume caused by varying the perfusion rates were apparent from the changes in volume in the oxygenator case and are shown graphically in Fig. 2. It will be noted that the changes in intra- and extracorporeal blood distribution were essentially the same in each instance. The consistency of the blood volume in each animal at each perfusion rate was striking.

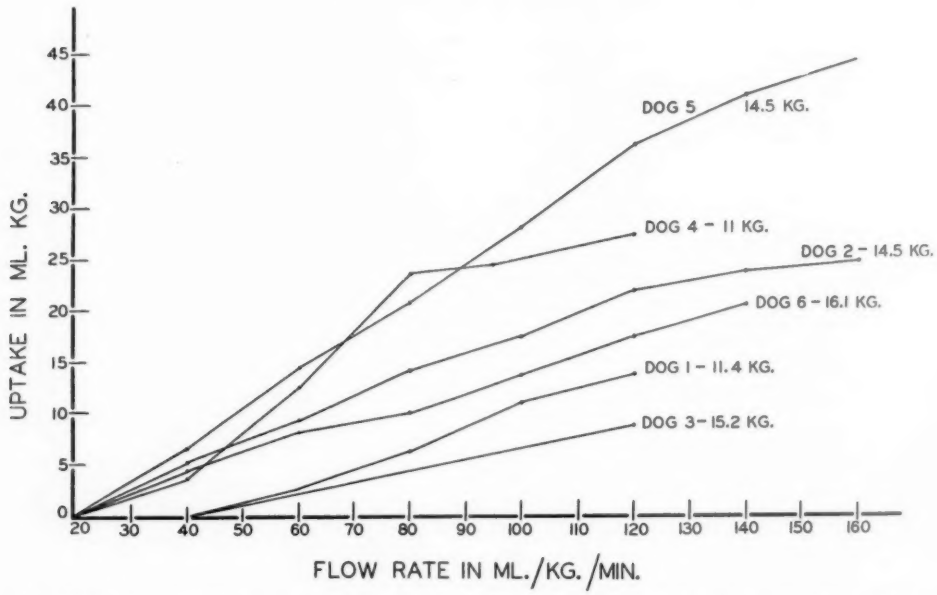

Fig. 2.—This shows the increase in the animal's blood volume as the perfusion rate was increased. (See text for additional remarks.)

We believe that 2 mechanisms of fundamental importance were demonstrated in these experiments: (1) The blood volume of the animal increased as the perfusion rate was increased. (2) There was a constant blood volume for each animal at each perfusion rate and this did not vary.

It should be noted that an essential condition of this experiment was maintenance of the venous pressure within the normal range (below 10 cm. H_2O). This excluded distention of the great veins with increasing perfusion rates and demonstrated that the portion of the intracorporeal circuit that accommodated the larger blood volume was proximal to the great veins.

Experiment 3. Effect of Hemorrhage on Blood Volume and Correlation With the Observations Made in Experiment 2.—

Procedure: The next step of obvious importance was to determine whether the conclusions drawn from Experiment 2 would be valid if there were sudden hemorrhage from the animal, causing a decrease in the total blood volume of the perfusion system. Four animals were bled from a femoral artery cannula into a graduated cylinder (Fig. 3), while the perfusion rate was kept constant and a normal venous pressure was maintained. The blood level in the graduated cylinder and in the oxygenator case was marked every 15 seconds. The volumes in the graduate could be read directly but the levels on the wall of the oxygenator case did not readily yield figures of similar accuracy because of the larger total volume, so precise measurements of the volume changes reflected by the marks made at 15-second intervals were carefully checked after the experiment was concluded. The same procedure was carried out in each of 4 animals.

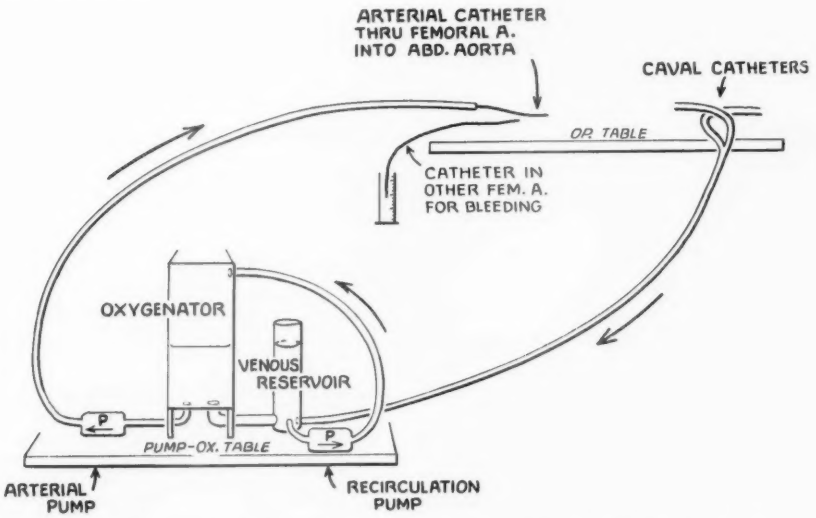

Fig. 3.—Diagram of experimental setup for measuring transfer of blood from oxygenator case to the animal as deliberate bleeding from a femoral artery was permitted.

Results: There was close correlation between blood loss from the femoral artery and the corresponding decrease in the volume of the oxygenator. The results of one experiment are shown in Fig. 4. It will be noted that the curves are quite similar, falling within the range of accuracy of the methods of measurement employed. Automatic replacement of blood loss by a shift of an approximately equal volume of blood from the oxygenator case to the patient occurred quite promptly and reliably. The slight delay in blood replacement in

some instances, both in regard to time and volume, may be due in part to technical limitations and in any event does not limit practical application significantly.

It seems justifiable to conclude that (1) the blood volume of the animal remained essentially constant in spite of rapid hemorrhage from a major artery, the blood loss being quite promptly and accurately replaced by automatic transfer of blood from the oxygenator case to the patient; and (2) rapid blood loss from the animal could not decrease the blood volume appreciably as long as the perfusion rate remained constant, the venous pressure low, and the blood level in the oxygenator case adequate to replace the volume lost.

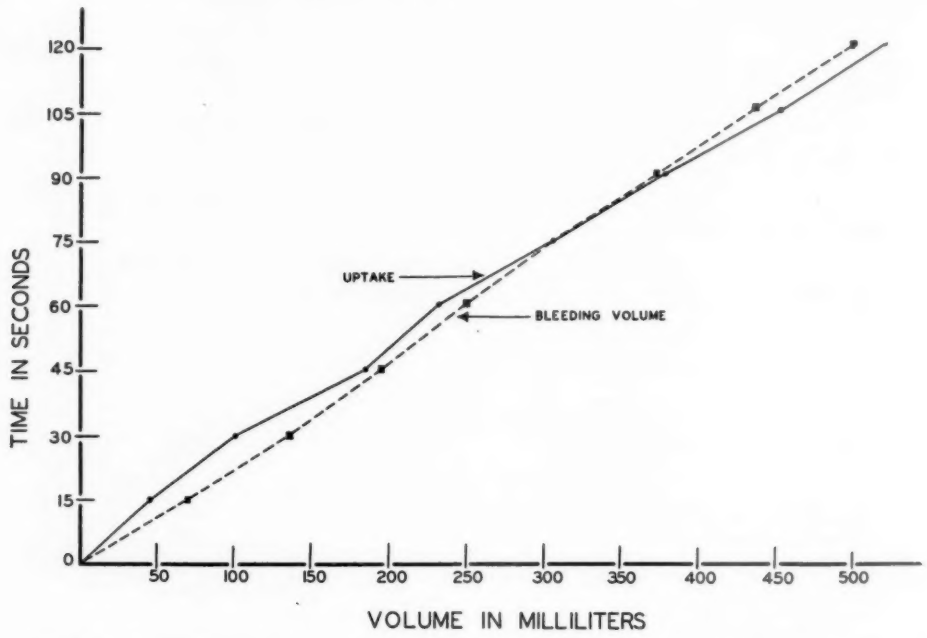

Fig. 4.—Correlation of blood loss and automatic replacement (uptake) from the oxygenator case in one experiment. The response was less prompt in some instances. (See text.)

Experiment 4. The Effects of Rapid Overtransfusion, With an Augmented Blood Volume and Elevated Venous Pressure, on Venous Distensibility and Other Factors Influencing Hemodynamic Readjustment When the Transfusion Was Stopped.—

Procedure: In considering clinical application, it seemed important to study the effects of acute venous distention and prolonged perfusion at high and low flow rates on the hemodynamic mechanisms demonstrated in previous experiments. After 3 dogs had undergone whole body perfusion at rates of 100 to 120 c.c. per kilogram per minute for 22 to 40 minutes, the blood volume was suddenly increased by giving rapid intravenous transfusions while at the same time partially occluding the caval drainage tubing just enough to maintain a constant blood level in the oxygenator case. The transfusion rates into the femoral vein were 10, 20, and 25 c.c. per kilogram per minute in the

respective animals. The venous pressure began to rise as soon as the transfusion was begun. Both the transfusion and partial caval outflow occlusion were discontinued when the venous pressure reached 40 cm. H_2O, which occurred in 4 minutes or less in all instances. After this procedure was carried out 2 or 3 times, the perfusion rate was changed to 20, 40, and 40 c.c. per kilogram per minute in the 3 dogs, respectively, and maintained for 60 minutes. The same transfusion test was then repeated in each of the animals at the low flow rates following which the experiments were terminated.

Results: A typical plot of venous pressure with respect to the increased blood volume caused by the transfusions, expressed in cubic centimeters per kilogram of body weight, is shown in Fig. 5. The curves were essentially the same in all 3 animals. When the partial caval occlusion was suddenly released, 90 per cent or more of the blood transfused into the animal promptly returned to the oxygenator case and the venous pressure rapidly fell to normal.

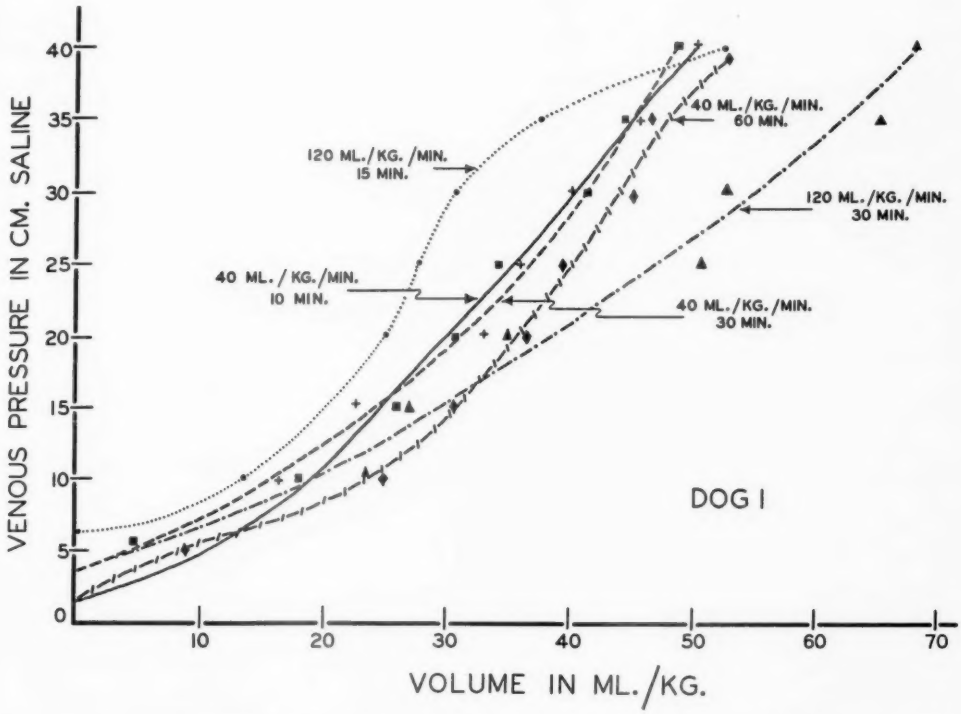

Fig. 5.—Increase in venous pressure caused by rapid overtransfusion. The curves were quite similar after imposing stress which might alter venous reflexes. (See text.)

These experiments appeared to demonstrate that the factors responsible for automatic maintenance of the animal's blood volume, described above, are not significantly altered by a sudden rapid increase in blood volume and venous pressure, at least for a period of 4 minutes. In addition, the venous distention caused by this sudden severe overload, which undoubtedly subjected the vein walls to rather violent sudden stretching, apparently caused no significant impairment of the functional characteristics which have been demonstrated to perform so reliably in maintaining an essentially constant

blood volume. It should be noted that the functional integrity of the veins was not affected apparently by a perfusion rate of 20 c.c. per kilogram per minute for 60 minutes. This would appear to be one aspect of vascular physiology which is not adversely affected by a subbasal perfusion rate for one hour. The observations of Alexander[1] suggested that there might be functional abnormalities under these circumstances.

Experiment 5. The Effects of Prolonged Periods of Fast and Slow Perfusion Rates on Blood Volume.—

Procedure: Whole body perfusion was carried out in 2 dogs at 120 c.c. per kilogram per minute for 12 and 35 minutes, respectively, and then the perfusion rate was decreased to 40 c.c. per kilogram per minute in both and maintained for one hour. During the periods of perfusion at both the high and low rates, however, an abrupt shift was made to the other perfusion rate for a brief interval, during which the new blood level in the oxygenator case was noted when stabilized, and the perfusion rate for this given period was then resumed. This experiment was designed as a further test of the thesis that each animal may be expected to maintain and repeatedly return to the same blood volume for any selected perfusion rate as long as the venous pressure does not exceed normal limits.

Results: The uniform return to the same blood volume when high and low perfusion rates were alternated after long periods are shown in the relatively constant volume changes noted in the oxygenator case in Table I.

TABLE I

PERFUSION RATE (ML./KG./MIN.)	TIME BEFORE CHANGING GIVEN PERFUSION RATE (MIN.)	VOLUME CHANGES WITH ALTERNATING PERFUSION RATES OF 120 AND 40 ML./KG./MIN. (ML.)
	Dog 1	
120	16	8.4
120	32	8.4
40	20	8.9
40	40	10.2
40	60	8.4
	Dog 2	
120	2	13.8
120	10	16.6
40	32	16.6
40	60	16.6

This experiment appears to provide strong evidence that the physiologic and mechanical factors which lead to a specific and characteristic actual blood volume at each perfusion rate are remarkably persistent, and also that these factors are not significantly altered by the many variations in the vascular tree which are brought about by shifting back and forth between high and low perfusion rates, and also by relatively long maintenance of a perfusion rate which is now regarded as rather low, that is, 40 c.c. per kilogram per minute.

Experiment 6. The Relationship Between Perfusion Rate and Arterial Pressure.—

Procedure: While making the observations concerning the relationship of blood volume and perfusion rate in Experiment 2, mean arterial pressure was recorded at the various flow rates and the figures were plotted separately to show the relationship between the arterial pressure and the rate of perfusion.

Results: The relationship is shown graphically in Fig. 6. In most instances there was not a directly proportional relationship between arterial pressure and perfusion rate.

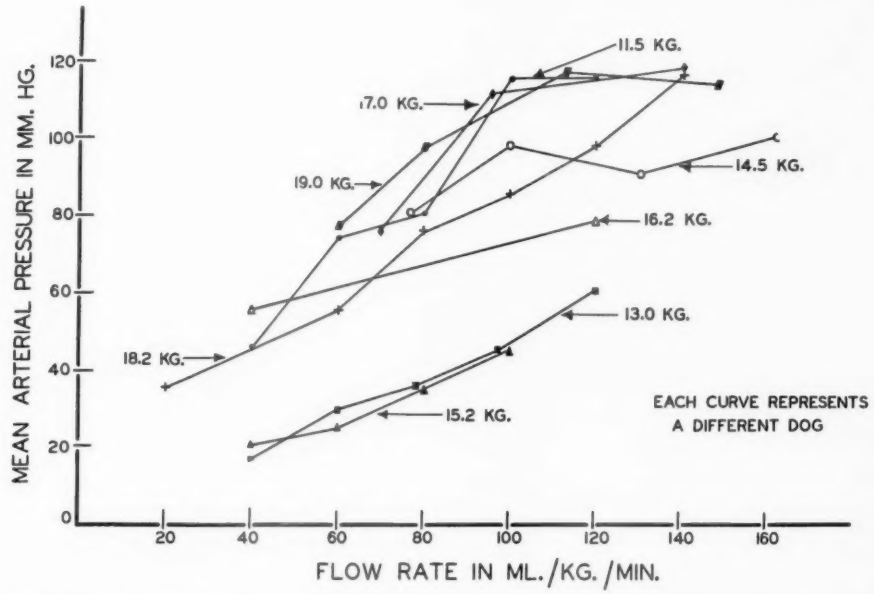

Fig. 6.—Mean arterial pressure plotted against increasing perfusion rates. (See text for comments.)

In general it may be concluded from these data and also from our experiences in perfusing patients that a certain percentile increase in perfusion rate is accompanied by a lesser percentile increase in the mean arterial pressure. Using the formula, total peripheral resistance $= \frac{\text{pressure}}{\text{flow}}$, the peripheral resistance was found to decrease as the perfusion rate was increased, except in 2 instances. It does not appear justifiable to speculate further about relationships to venous pressure and other aspects of the vascular reflex mechanisms on the basis of these studies.

APPLICATION OF THESE OBSERVATIONS TO CLINICAL PERFUSION FOR OPEN HEART SURGERY

We believe it has been demonstrated in these experiments that the blood volume of the patient may be accurately controlled during the period of

cardiac bypass without attempting to measure blood loss from all sources at intervals of 1 to 5 minutes and replace it by transfusion either into the patient or the extracorporeal circuit.

Application of this method of automatic blood volume control has been highly satisfactory in patients. Certain factors are of critical importance in the successful application of this principle and we believe that they may be briefly outlined:

1. A perfusion rate approximately equal to the basal cardiac output of the patient should be chosen. From 2 to 2.2 L. per square meter per minute has appeared satisfactory in our clinical experience, which is not yet large enough to justify generalizations concerning patients with an abnormally large blood volume and high cardiac output due to large shunts.

2. The caval catheters should be large enough and the height of the right atrium above the blood level in the venous reservoir should be great enough to insure that the venous pressure is normal. An excessive caval outflow gradient may produce caval flutter.

3. The level in the oxygenator case is marked just before starting the perfusion (Mark 1) and again when stabilization has occurred after going on total bypass (Mark 2). The perfusion rate chosen for the patient is attained by turning up the arterial pump rate to the calculated speed very quickly after releasing the clamps leading to and from the extracorporeal circuit. The level in the oxygenator case has usually risen after perfusion has begun, but it seems clear from animal experiments that the level may remain constant or even fall a little if the perfusion rate exceeds the patient's preperfusion cardiac output.

4. The level in the priming reservoir is marked at the beginning of the perfusion. The level in the oxygenator case gradually falls as the procedure progresses and automatic replacement of blood lost by the patient occurs. Blood is gradually permitted to enter the oxygenator case from the priming reservoir as the level falls and blood is not added to the extra- or intracorporeal circuit by any other route during perfusion. Just before the termination of total cardiac bypass, the level in the oxygenator case is brought back to the initial level at which stabilization occurred (Mark 2). Then the caval tapes are released and the caval outflow tubing is partially constricted while the level returns to the mark made before the perfusion was begun (Mark 1). The blood volume of the patient is thus restored to the preperfusion level. The volume of blood added through the priming reservoir is then regarded as blood transfused into the patient. Blood loss is measured as in any other operation, that is, blood loss in the suction bottles, on the sponges, and so forth, and blood loss is not considered to be associated with the pump-oxygenator as a separate item. The only figure used in calculating the blood balance, therefore, is the amount of blood added to the priming reservoir during cardiopulmonary bypass.

5. Discontinuing first total and then partial bypass is usually not difficult. As stated above, the blood level in the oxygenator case is brought back to the

mark made when stabilization on total bypass occurred. This is usually a little above the preperfusion level. Ordinarily the heartbeat is strong and the perfusion can be stopped after a very short time (less than a minute) on partial bypass. During this time the venous outflow tubing is partially occluded, permitting more blood to pass through the heart and lungs, so that the level in the oxygenator case returns to the preperfusion level. As more blood enters the heart, the stroke volume of the left ventricle increases and the arterial pressure tracing, which shows mean pressure as almost a straight line during total bypass, again shows characteristic pulsations. It seems advisable to make the period of partial bypass brief because the experiments described above were performed during total bypass, and the blood volume relationships may be altered when an unknown portion of the caval return passes through the heart.

If the heartbeat is not effective enough to provide adequate unassisted circulation immediately, a gradual "weaning" away from the support of partial bypass may be necessary. This has been uncommon in our experience, and the complex blood volume changes cannot be discussed here.

In some instances, changes in the level in the oxygenator case may be due, in part, to changes in the volume of the systemic vascular bed. Additional studies which should clarify this point are being performed. The absence of alterations in the distensibility characteristics (Experiment 4) and the repeated return to approximately the same blood volume after prolonged periods (Experiment 5) suggest that any change in the systemic vascular bed is not great, even following perfusion at relatively low flow rates.

CONCLUSIONS

Hemodynamic mechanisms which permit automatic maintenance of a relatively constant blood volume during cardiopulmonary bypass and the experimental observations on which this concept is based have been described. This method has greatly simplified the problem of blood volume control during open heart surgery in patients. The details of clinical application have been outlined.

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FUNCTIONAL POPLITEAL PHLEBOGRAPHY IN THE PATIENT WITH A COMPLICATED VARICOSE VEIN PROBLEM

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THE superficial veins of the lower extremity are readily accessible for evaluation. Anatomic variations or pathologic changes can be determined by a careful inspection. Functional tests like the Trendelenburg enable one, in general, to determine the position of incompetent valves or perforators. The deep veins, however, are encased in their muscular pump beneath the fascia of the leg. A thorough evaluation of these deep veins is dependent upon their visualization, which can best be accomplished with phlebography.

Numerous techniques for the performance of phlebography have been described since Berberich and Hirsch[2] first injected radiopaque material into the superficial veins of human beings for radiographic examination. Techniques based upon the injection of radiopaque dye into the popliteal vein have undergone several refinements. Robertson, Share, and McGovern,[6] and also Szilagyi and Alsop[11] independently first utilized the lesser saphenous vein to inject the radiopaque material directly into the popliteal vein. Robertson, Share, and McGovern[6] delayed emptying of the dye from the deep system by tilting the patient from a horizontal to a vertical position as they made their injection. Ferreira, Villamil, and Ciruzzi[4] modified this approach by maintaining the patient in a semi-erect position of 45 degrees from the horizontal but taking x-rays immediately after injection and again after the patient had raised himself on his toes 2 times. In this fashion, they evaluated the functional ability of the venous system as well as its anatomic or pathologic condition. Schumacker, Moore, and Campbell[9] described a similar type of functional venography. They injected the dye percutaneously directly into the popliteal vein with the patient tilted 60 degrees from the horizontal position and took x-rays before and after the patient had raised himself 10 times on his toes.

We have selected a method of functional phlebography similar to that described by Ferreira to study the deep veins of the lower extremities of 36 patients. The method was initially evaluated on patients with known normal and abnormal deep veins. Twenty patients with complicated varicose vein problems were then studied to determine the status of their deep veins.

METHOD

The lesser saphenous vein is exposed in the upper one-third of the calf and a polyethylene catheter is threaded superiorly about 15 cm. so that the catheter lies in the popliteal vein. The patient is then transferred to the x-ray

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table where he lies in a prone position. The foot of the x-ray table is then tilted down to 45 degrees from the horizontal. A 14 by 17 inch x-ray film is centered at the knee joint. Twenty-five milliliters of suitable contrast material* is then injected over a 20-second period and the film exposed at the end of the injection. The patient then raises himself forcefully on his toes 3 times and a second x-ray is taken within about 15 seconds of the first. Another 20 ml. of dye is then injected and a third x-ray is taken of the upper thigh. Recently, we have placed two 14 by 17 inch films lengthwise under the entire leg and taken only 2 x-rays, one before exercise and one after exercise.

Fig. 1.—C. G. Normal extremity. Normal appearing and well functioning deep veins. Popliteal (*a*), anterior tibial (*b*), posterior tibial (*c*), peroneal (*d*). Following exercise (middle film), the dye has disappeared from the veins except for a small amount trapped in the cusps of the valves. The last film demonstrates a normal femoral vein (*e*). Normal valves are well demonstrated.

EVALUATION OF METHOD

Phlebograms were performed on 16 patients in whom the status of the deep veins was predictable on the basis of a careful history and physical examination. Five patients with mild and relatively asymptomatic superficial varicose veins and 11 patients with probable attacks of deep vein thrombosis in the past underwent the examination (Table I). The patients with superficial varicose veins of a minor nature all had normal appearing and normal functioning deep veins (Fig. 1). Anatomically, the veins were smooth walled and had well-defined valves. Functionally, the dye initially refluxed down the popliteal vein and commonly down the anterior tibial, posterior tibial, or peroneal veins to as far as 3 valves below the joint line, but following exercise the popliteal and calf veins contained little dye except for small amounts trapped behind the

*The contrast materials used were either 35 per cent Diodrast which had a specific gravity of 1.195 or 30 per cent Urokon which had a specific gravity of 1.208.

valvular cusps. The 11 patients with previous deep vein thrombosis had abnormal appearing and poorly functioning deep veins. Some deep veins had segmental areas of obstruction. Others had irregular walls, were valveless, and were incompletely filled with dye, suggesting recanalization (Fig. 2). In 2 instances, we noted long segments of apparently obstructed veins which were bordered by parallel thin irregular lines of dye (Fig. 3). Although it is conceivable that recanalization of the periphery of the vein could explain this appearance, a more plausible explanation to us is that this represents collateral

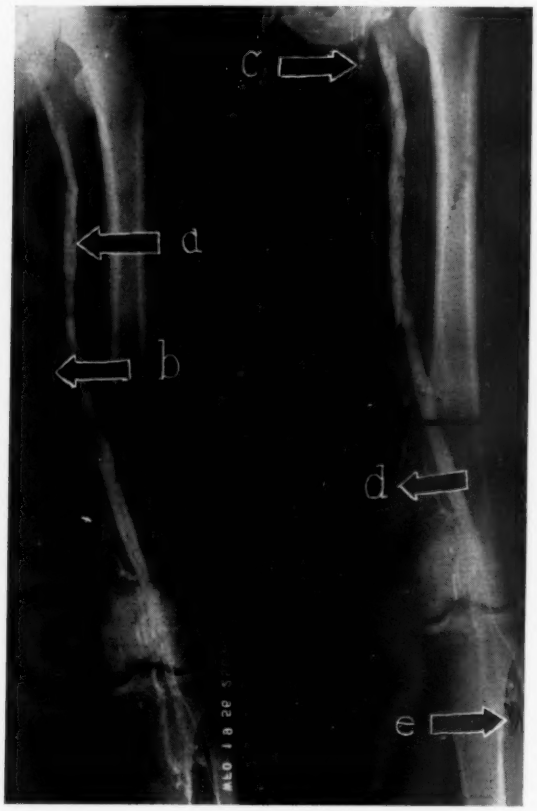

Fig. 2.

Fig. 3.

Fig. 2.—P. T. Postphlebitic extremity. Abnormal appearing and poorly functioning deep veins. Incompetent perforators. The first film demonstrates the irregular valveless walls and apparent filling defects (*a*) of the recanalized deep veins. An incompetent perforator (*b*) is also visible. The second film, after exercise, demonstrates no emptying and further reflux of the dye in the deep veins (*e*). An incompetent perforator (*d*) is also visible.

Fig. 3.—B. T. Postphlebitic extremity. Abnormal appearing and poorly functioning deep veins. Incompetent perforators. The first film demonstrates 2 tortuous veins which parallel the course of the blocked femoral vein and probably represent collateral venae comitantes (*b*). A dilated tortuous communication between the lesser saphenous and femoral vein (*a* and *c*) is seen. The second film, after exercise, demonstrates poor emptying of the deep veins and also further reflux down the deep veins (*d* and *e*). Incompetent perforators filling tortuous superficial veins are also visible.

venae comitantes and that the main vein is now obliterated. Dilated collateral veins were frequently seen. The absence of normal appearing valves was a finding common to all of the above changes. In abnormal appearing veins, abnormal function was also noted. The veins did not empty well with exercise and in some instances further reflux of dye down the main channels was noted (Figs. 2 and 3).

TABLE I. PHLEBOGRAPHIC FINDINGS IN NORMAL AND POSTPHLEBITIC EXTREMITIES

HISTORY	NUMBERS	INTERPRETATION OF PHLEBOGRAMS	
		ANATOMIC	FUNCTIONAL
Mild varicose veins	5	Normal	Good
Previous deep phlebitis	11	Abnormal	Poor

STUDY OF PATIENTS WITH COMPLICATED VARICOSE VEIN PROBLEMS

Twenty patients with complicated varicose vein problems were studied by phlebography. These patients all had numerous superficial varicosities with associated stasis dermatitis. Eighteen had persistent swelling of significant degree. Nine had had previous superficial vein surgery. Twelve had had indolent ulcers or had ulcers at the time of the examination. None of these patients gave a history suggestive of deep vein thrombosis preceding nor during the course of their varicose vein problems.

Fig. 4.—W. O. Complicated varicose vein problem. Normal appearing and functioning deep veins. Incompetent perforators and normal functioning superficial veins. The first film demonstrates filling of normal deep veins except for an abnormal communication between the superficial and deep femoral veins (*a*). The second film, after exercise, demonstrates very good perforators (*b* and *c*) which lead to dilated, tortuous superficial veins in which reflux of the dye has occurred with exercise. (Picture retouched for clarity.)

The results of these studies are summarized in Table II. In 6 of the patients the deep veins appeared normal and the popliteal vein emptied well after exercise, but incompetent perforators and a poorly functioning superficial system were visualized (Fig. 4). Communications between the deep and superficial system were initially considered incompetent perforators only if the dye refluxed from the deep to the superficial veins. Such perforators, however, were in general dilated and tortuous veins and we now feel that such an appearance

signifies an incompetent perforator. The superficial veins visualized were, in general, dilated and tortuous, but the striking finding was the reflux of the dye in the superficial veins after exercise.

Fig. 5.—J. H. Complicated varicose vein problem in a 59-year-old man. Deficiency of valves in deep veins which function poorly. Incompetent perforators. The first film demonstrates filling of deep veins which are deficient in valves. A communication between the lesser saphenous and greater saphenous veins is seen. The second film, after exercise, demonstrates poor emptying of the deep veins. The dye refluxes through incompetent perforators (*a* and *b*) with exercise. The last film demonstrates a deficiency of valves in the femoral vein There is also a tortuous, dilated perforator (*c*). (Picture retouched for clarity.)

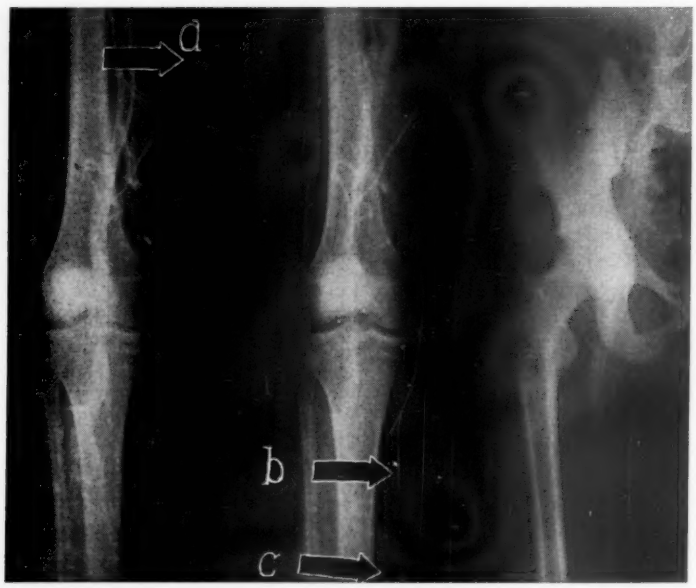

Fig. 6.—R. F. Complicated varicose vein problem in a 16-year-old boy. Deficiency of valves and poorly functioning deep veins. The first film demonstrates filling of the popliteal and calf veins and also a communicating vein between the lesser and greater saphenous veins (*a*). Following exercise (middle film), there is still dye in the popliteal and calf veins and also reflux down superficial veins (*b* and *c*). (Picture was retouched for clarity.) Note the scarcity of the valves until the dye descends into the veins and the dilatation of the popliteal vein. The last film demonstrates a straight-walled valveless femoral vein.

TABLE II. PHLEBOGRAPHIC FINDINGS IN PATIENT WITH COMPLICATED VARICOSE VEIN PROBLEMS

PATIENTS STUDIED	DEEP VEINS		INCOMPETENT PERFORATORS	SUPERFICIAL SYSTEM (FUNCTION)
	ANA	FUNCTION		
6	Norma	Good	Present	Poor
7	Abnor	Poor	Present	Poor
2	Abnormal	Poor	Not visualized	Not visualized
5	Normal	Good	Not visualized	Not visualized

Seven of the patients had abnormal appearing deep veins, poor emptying of the dye from the popliteal vein after exercise, incompetent perforators, and poorly functioning superficial veins (Figs. 5 and 6). The deep vein abnormalities noted in this group of patients included deficiency of valves and dilatation of the veins. The deficiency of valves extended over long segments of the vein and included the entire superficial femoral and/or the popliteal veins. One patient had dilatation with apparent valves. It is interesting that, although most of these patients were older patients with a history of having had varicose veins for only 10 to 15 years, there were 2 patients, 16 and 27 years of age, who had noted severe varicosities of their legs since early childhood. The deep vein abnormalities in this group of patients were not at all similar to those seen in the patients with old deep vein thrombosis. The one common finding was that neither group had normal valves. It was not surprising, therefore, that these deep veins also emptied poorly with exercise.

Two of the patients had abnormal appearing deep veins and poor emptying of the popliteal vein, but no incompetent perforators nor superficial veins were visualized.

Five of the patients had normal deep veins and good emptying of the popliteal vein, but no superficial veins were visualized. Although the failure to demonstrate known incompetent perforators in the thigh in 2 of these patients was disconcerting, it should be re-emphasized that the purpose of this method of phlebography is to study the deep veins of the leg.

DISCUSSION

The evaluation of this method of phlebography on relatively normal and postphlebitic extremities gave us some valuable basic information. It gave us an opportunity to visualize the normal appearance of the deep veins of the thigh and upper calf. It also gave us an opportunity to visualize the results of a deep vein thrombosis. We were impressed by the fact that in the postphlebitic extremities neither recanalized veins nor dilated deep collateral veins had apparent valves.

The observation that normal appearing deep veins emptied well and that valveless deep veins did not empty well with vigorous contraction of the gastrocnemius muscle 3 times was a valuable one to us. Ferreira[4] made the same observation with contraction of the gastrocnemius muscle 2 times. Shumacker,[9] however, observed that even abnormal recanalized deep veins emptied after contraction of the gastrocnemius muscle 10 times. He implied that such veins are not very abnormal functionally. It should be pointed out, however, that venous stasis

is only relative. In the presence of a normal heart and in absence of any acute obstruction of the deep venous system, the standing pressure in any vein is very nearly equal to the distance between the vein and the right atrium. These pressure relationships are present in normal legs, legs with severe superficial varicosities, and those with the postphlebitic syndrome.[5] It is only with ambulation that differences in pressure between the normal and abnormal veins can be noted. Whereas the pressure in a normal vein will decrease rapidly with walking and then return slowly to normal, the pressure in the vein of a diseased venous system will decrease less over longer periods and return rapidly to normal.[3, 5, 12] A person who has a standing job is likely to perform exercise equivalent to contracting their gastrocnemius muscle 2 or 3 times, several times during an hour period. If their veins are normal they will have frequent periods when the pressure in their venous system is decreased. If they have valveless veins for any reason, these periods will occur less frequently and to a lesser degree, and they will have a relative venous stasis. Consequently, it seems important to us that, in performing a functional study of the veins, one uses an exercise sufficiently mild to differentiate between normal and abnormal veins. Our method fulfilled this criterion.

The contrast material used had a specific gravity greater than that of blood. The apparent retrograde filling of the calf veins in both abnormal and normal deep veins at rest was at least partially due to the settling of the heavier dye. With exercise the heavier dye is probably not propelled at the same rate as blood but still reflects movement of the blood. Normal deep veins were more readily emptied of dye, and therefore blood, than abnormal deep veins with the same standard exercise. Therefore, despite the heaviness of the dye, this method still differentiates normal veins from abnormal deep veins.

In studying the group of patients with complicated varicose vein problems, we again noted deep veins which emptied poorly with exercise. This poor function correlated well with an abnormal appearance of the deep veins. These deep vein changes were unlike those seen in the postphlebitic veins. Dilatation was a common finding but the deficiency of visible valves was a more consistent finding. These changes are similar to those described as "idopathic valvular incompetence" by Bauer.[1] The fact that these changes were noted in young men with known severe superficial varicosities since childhood suggests that in some instances these may be congenital abnormalities. The fact that similar changes were noted in older patients with relatively short histories of varicose vein problems suggests that the same changes may be degenerative change.

Although we have demonstrated the incompetence of the valveless deep veins in the patient with the postphlebitic syndrome and in certain patients with complicated varicose vein problems, we do not feel that this incompetence justifies ligation of the deep veins. Collaterals must form around the site of ligation, and the dilated tortuous collaterals we have visualized are also incompetent. It is not surprising that advocates of deep vein ligations in the treatment of the lower leg syndrome have retracted their earlier more enthusiastic reports.[3, 10] On the other hand, we have utilized the results of our phlebographic studies to advocate an even more conservative approach to the management of

severe lower leg problems. For the past several years, patients with the postphlebitic syndrome, particularly those with ulcers, have had nonoperative management. The usual conservative measures of elevation, control in infection, and control of dermatitis have been used. In addition, a more adequate lower leg compression by means of an Aero-pulse legging has been utilized.[7, 8] We are now advocating the same nonoperative management of those patients with severe varicose vein problems in whom we demonstrate abnormal appearing and poorly functioning deep veins. We feel that these patients are the ones who are most likely to have continued venous stasis problems despite adequate superficial vein excisions. This concept is supported by the fact that, of the 5 patients over 30 years of age who had deep vein abnormalities demonstrated by phlebography, 4 of them had had previous superficial vein surgery.

Patients who have normal appearing deep veins but have varicose veins, however, should benefit from adequate superficial vein ligations, strippings, and ligations of incompetent perforators.

SUMMARY

1. A method of performing functional phlebography of the lower extremity has been described.

2. Evaluation of the method indicates that it can adequately differentiate normal deep veins from abnormal deep veins anatomically and functionally.

3. Application of the method to patients with complicated varicose vein problems enables one to diagnose deep vein abnormalities in many of these patients. These abnormalities may be congenital valvular defects, degenerative valvular defects, or unsuspected postphlebitic changes.

4. The phlebograms can assist the surgeon in selecting a logical form of therapy for the patient with a complicated varicose vein problem.

I would like to acknowledge the helpful advice and criticisms of Dr. W. J. Merle Scott in carrying out this project.

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THE EFFECTS OF ARTERENOL ON BLOOD PRESSURE AND VENOUS RETURN DURING EXTRACORPOREAL CIRCULATION

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THE application of extracorporeal techniques to open heart surgery has stimulated interest in the basic problems associated with these methods. Many workers using these techniques believe that for short periods of time the vital structures of the body can subsist on blood flows considerably less than normal, but most persons would agree that from a metabolic viewpoint the more nearly normal the flows, the better for the patient. Thus, one of the aims of investigators in this field has been to develop methods of obtaining more physiologic flows without multiplying the technical and mechanical difficulties of the perfusion method.

In a previous publication,[5] it was shown that there is a direct relationship between blood volume and available venous return during total cardiopulmonary bypass. This was established by measuring flow through an extracorporeal circuit in splenectomized dogs at various blood volumes, as determined by a tagged red blood cell technique. It was shown that there is a wide variation in flow at comparable blood volumes in different animals. The average flow-volume curve is shown in Fig. 1. Because of the wide range of flows at comparable blood volumes, it is not possible to predict flow from a known blood volume; however, it is clear that the chances of obtaining greater venous return, and therefore greater perfusion rates, are best with normal or greater than normal blood volumes in any individual instance.

As previously noted, the similar "stair-step" shape of the individual flow-volume curves led us to reason that there must be relatively few factors influencing this relationship, and the most likely explanation seemed to be the response of the vasomotor system to changing blood volume.

If changes in vasomotor tone are responsible for these changes in the flow-volume response, then agents affecting vasomotor tone should have an effect upon venous return. Smyth and associates[8] have shown that arterenol (Levophed) increases splanchnic resistance and postulate that increased tone in the postarteriolar bed in effect transfers blood back into the general circulation. Fowler and co-workers[3] have concluded that arterenol also increases peripheral venous constriction. The result of these effects would be a relative increase in blood volume with respect to the available vascular space.

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The following experiments were designed to study the effect of arterenol upon available venous return during extracorporeal circulation with various degrees of blood volume depletion and expansion.

METHOD

Blood volume was determined in all instances by a tagged red blood cell method using Cr^{51}.[2] Bonnycastle[1] has reported that, during barbiturate anesthesia in dogs, there is an increase in plasma volume and a decrease in red blood cell mass. Since a tagged red cell technique was to be used to determine blood volume, the spleen was removed from all the animals used in these studies. This was based upon the assumption by Bonnycastle that the spleen was responsible for the changes in red cell mass during anesthesia.

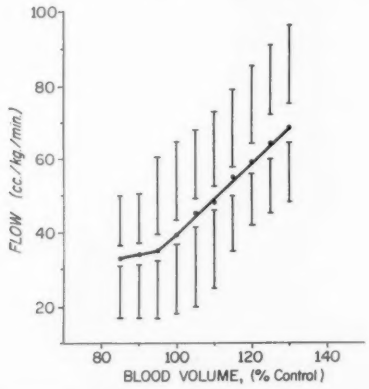

Fig. 1.—The average extracorporeal flow at various blood volumes. The brackets indicate the ranges at each blood volume.

Control blood volumes were performed on all the dogs after complete recovery from the splenectomy. Approximately one week following the determination of control blood volume, each dog was cannulated for extracorporeal circulation with a No. 18 French catheter in each vena cava for venous return and a No. 16 French catheter in one femoral artery for perfusion.[6] When these preparations were complete, an operative blood volume was performed for comparison with the control. When the necessary samples for blood volume determination had been obtained, the extracorporeal circuit was established and the venous return at this initial blood volume determined, using collapse of the caval walls as an index of total removal of venous blood.

Arterial pressure then was elevated to preperfusion levels with a slow intravenous drip of concentrated Levophed (12 c.c./100 c.c. saline) and any increase in venous return noted. Blood volume then was expanded by rapid transfusion of 100 c.c. increments of whole blood and venous return at each new blood volume measured, while blood pressure was maintained with the Levophed infusion.

RESULTS

Flow-volume curves were produced by plotting available venous return (cubic centimeter per kilogram per minute) against blood volume, which was expressed as a percentage of the control value for each animal.

Fig. 2 demonstrates 4 such experiments. In 3 of them the initial portion of the curve is represented by a straight vertical line. This represents the increase in venous return after elevating the arterial pressure to normal with Levophed without increasing blood volume. In the fourth animal there was no significant change initially, but the initial venous return was high (53 c.c. per kilogram per minute).

Fig. 3 shows the flow-volume curves for these 4 experiments superimposed upon the average flow-volume curve determined without the use of vasopressors. The shaded area is the range of flows at the various blood volumes and the line in the center of this shaded area is the average flow curve.

It is felt that the 4 experiments done with arterenol show significantly higher flows at comparable blood volumes than do the averages.

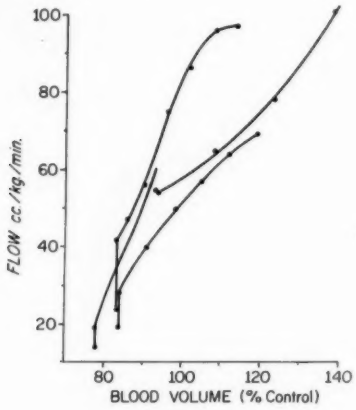

Fig. 2.

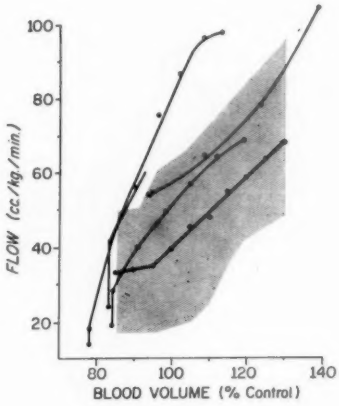

Fig. 3.

Fig. 2.—Four experiments demonstrating extracorporeal flow at various blood volumes, while arterial pressure is maintained with Levophed.

Fig. 3.—The extracorporeal flows during Levophed administration are superimposed on the average curve to show that greater flows are obtainable at comparable blood volumes.

The administration of the vasopressor during these studies accomplished two things which may be important clinically. First, it elevated the perfusion pressure, which may be of advantage, and, second, it apparently increased available venous return and allowed increased perfusion rates. The most likely explanation for the effect upon venous return seems to be that, by producing arteriolar and venous constriction, it increases the relative blood volume with respect to the available vascular space.

While accomplishing these two things, the administration of Levophed should have no adverse effect upon cerebral blood flow. Schmidt[7] has said that present evidence would indicate that the cerebral vessels are relatively insensitive to known vasoconstrictors in physiologic doses. The isolated perfusion experiments of Green and Denison[4] in dogs support this idea.

CONCLUSIONS

1. The available venous return has a direct relationship to blood volume.

2. Elevation of perfusion pressure by the administration of arterenol is associated with an increase in available venous return at nearly all levels of blood volume depletion or expansion measured.

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PARASITIZATION OF ISOLATED SMALL BOWEL LOOPS IN DOGS

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THE replacement of anatomic structures of affected organs with healthy tissue offers one of the most interesting aspects of surgical technique. During the last decade, considerable experimental research has been conducted along these lines. Viable intestinal segments or other tissue were used for plastic operation on the urinary bladder (Barnes and associates,[1] Hammer and associates,[7] Nissen,[11] McLean and Fais,[10] and Baum[2]). The tracheobronchial defects were corrected with tissue grafts (Gebauer,[5] Jackson and associates,[9] and Taffel[13]). Several reports were published on esophageal replacement by jejunum in connection with its influence upon mesenteric vessels (Schumacker[12]). An attempt was made on rabbits to keep a segment of intestine viable with a single blood vessel attached (Galluzzi[3, 4]). Viable intestinal segments were used experimentally as internal pedicle flaps to replace or reinforce viable structures in the abdomen. In this method, the intestine was split open longitudinally, the mucosa was removed and the wall was used as a viable graft (Hammer and associates[6]). If an anterior abdominal wall defect is repaired, the blood vessels of the flap act as a band about which a bowel loop twists. According to Hill and Hammer,[8] the mesentery can be divided at a later date after the graft takes. This work, however, does not involve the preservation of the bowel as a viable tube for the restoration of the gastrointestinal tract in continuity. There seems to be no experimental work published so far on parasitization of the small bowel to the abdominal wall.

It is well known that massive small bowel resections, with their deficiencies in absorption, have resulted in the gradual deterioration of the patient's condition. Under certain instances of nonemergency resection of the small bowel and right colon, it is feasible to create, at a first stage, an isolated loop of small bowel, parasitized on the abdominal wall. It is also feasible, at a second stage, to interrupt the blood supply to the isolated segment. It is also quite possible to remove the intraperitoneal small bowel and right colon and to anastomose the isolated loop to the duodenum and it, in turn, to the colon. However, that the parasitized isolated loop of small bowel is viable does not necessarily mean that it has retained its absorptive function and that it could physiologically replace the resected small bowel.

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The purpose of the present experimental study is to demonstrate that an isolated loop of small bowel can be devascularized after transplantation to the abdominal wall, and that the gastrointestinal continuity can be restored, using the parasitized bowel, after resection of the major portion of the small bowel in dogs.

METHODS

Adult mongrel dogs were used in these experiments. Under general pentobarbital anesthesia, the abdomen was opened and a segment of small bowel varying between 15 and 30 cm. in length was isolated and the bowel transected. The proximal and distal ends of the bowel were then anastomosed end-to-end, in order to restore gastrointestinal continuity. The isolated loop of small bowel was brought out through a small opening in the abdominal wall, very carefully, in order to preserve its blood supply and not create any compression or venous engorgement. The isolated loop was then placed in the subcutaneous tissue of the abdominal wall and its ends brought out through stab wounds in the skin. The mucosa of the bowel was sutured to the skin of the abdominal wall. At the end of the operation, the isolated loop of small bowel lay subcutaneously with both ends open and the only attachment to the peritoneal cavity was the mesentery with its blood supply. Either jejunum or ileum was used in the dog. In 2 dogs it was possible to create 2 separate isolated loops of small bowel, each 20 cm. long; one from the upper jejunum and the other from the lower ileum.

About one month after the initial surgery, the animals were re-explored and the pedicle of the mesenteric blood vessels to the isolated loop was transected and ligated. The animals survived this well. About 1 or 2 months after the second operation, the dogs were re-explored and a resection of 90 per cent of the intraperitoneal small bowel was carried out and the duodenum was anastomosed to the upper end of the isolated subcutaneous loop. The distal end of the subcutaneous loop was anastomosed to the terminal ileum. In this way the continuity of the intestinal tract was restored.

EXPERIMENTAL PROCEDURE

In one group of animals (Table I), an isolated loop of jejunum or ileum was created as the initial procedure. In 3 of the dogs, isolated loops of jejunum 20 cm. in length were created and about one month later, the isolated loop's blood supply was transected. One animal died immediately postoperatively and autopsy showed massive atelectasis due to aspiration of gastric contents. The other 2 dogs were observed and the isolated loops were found to be viable for the 2 months of observation. The mucosa did not change in color and the animals were afebrile. The abdominal wall did not become infected. There was no change in the amount of mucous discharge from the intestinal lumen. Passage of methylene blue was unchanged and the small bowel loop had retained its motility. Various dyes, such as methylene blue, were absorbed and excreted in the urine.

TABLE I. ISOLATED SMALL BOWEL SEGMENT WITH LIGATION OF BLOOD SUPPLY

DOG	WEIGHT (POUNDS)	SITE OF ISOLATED LOOP	LENGTH OF LOOP	DATE OF LOOP	DATE OF LIGATION OF PEDICLE	TIME OBSERVED
X-A	25	Jejunum	15 cm.	10/10/56	11/12/56	1 month
X299	25	Jejunum	25 cm.	10/10/56	11/12/56	1 month
X218	18	Jejunum	25 cm.	10/15/56	11/19/56	Died from atelectasis
X136	28	Upper jejunum	20 cm.	11/31/56	—	Died postoperatively, torsion of pedicle
		Lower ileum	20 cm.	11/31/56	—	
X247	28	Upper jejunum	20 cm.	11/ 5/56	1/ 7/57	3 months
		Lower ileum	20 cm.	11/ 5/56	1/ 7/57	

In 2 other dogs, a double isolated loop was created. The upper one originated from the upper jejunum and the lower one from the distal ileum. Each loop was about 20 cm. long. Intestinal continuity was restored intraperitoneally leaving both loops isolated subcutaneously except for the vascular pedicle to each loop. One dog died 3 days postoperatively because there was torsion of the vascular pedicle with gangrene of the loops. This dog served as a control to the experiment showing that a period of time is needed for parasitization of the bowel to the abdominal wall. The second animal survived the initial procedure and the vascular pedicles to both isolated loops were ligated about 2 months later and the subcutaneous loops of bowel remained viable and healthy in appearance. The mucosa retained its normal color and the dog remained well. Methylene blue was absorbed from the isolated loops and was disclosed in the urine. When the animals were sacrificed about 3 months later, the small bowel was found to be viable and the lumen patent.

In another group of dogs (Table II), the isolated loop of jejunum about 30 cm. in length was created and brought out subcutaneously in the abdominal wall. About one month later, the vascular pedicle was ligated without ill effects and the transplanted bowel remained viable. One month following this second procedure, the dogs were re-explored and over 90 per cent of the small bowel was resected and the duodenum was anastomosed to the upper end of the isolated loop and the distal end of the loop to the terminal ileum. One animal survived 5 days; the other animal 12 days. The first dog died of a leak at the proximal anastomosis with peritonitis. The second animal died of inanition and malnutrition and diarrhea.

TABLE II. ISOLATED SMALL BOWEL LOOP WITH LIGATION OF BLOOD SUPPLY AND MASSIVE RESECTION OF SMALL BOWEL

DOG	WEIGHT (POUNDS)	SITE OF ISOLATED LOOP	LENGTH OF LOOP	DATE OF LOOP	DATE OF LIGATION OF PEDICLE	DATE OF MASSIVE RESECTION	RESULT
X165	20	Jejunum	30 cm.	10/22/56	11/14/56	12/17/56	Died 5 days postoperatively, peritonitis
X-B	32	Jejunum	30 cm.	1/18/57	2/25/57	4/15/57	Died postoperatively, malnutrition, 12 days

DISCUSSION

The concept of transplanting the small bowel to bridge defects in the urinary tract or in the gastrointestinal tract is not a new one. On the other hand, the possibility of parasitizing the small bowel in long segments to the abdominal wall and severing its blood supply in stages is novel. These experiments demonstrate that the devascularization of a transplanted loop of small bowel in the abdominal wall is feasible and practical. In one month's time, the isolated segment of bowel derives enough blood supply from the surrounding subcutaneous tissue that it remains viable when the vascular pedicle is severed. When the pedicle is cut, the isolated loop still secretes mucus and can absorb vital dyes. The mucosa of the isolated loop remains viable and the animal survived the operation satisfactorily. The third stage in the experiment is not an easy one. The resection of the small bowel with re-establishment of intestinal tract continuity, using the isolated small bowel loop, was fatal to one dog. He died of an anastomotic leak. The other dog survived the immediate postoperative period but died of malnutrition.

CONCLUSIONS

1. Isolated loops of small bowel were parasitized to the abdominal wall successfully in 7 dogs.

2. The parasitized isolated small bowel loop in the dog appeared to manifest absorptive potentialities and therefore can be used for restoring intestinal continuity in the event of a small bowel resection.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

PHYSIOLOGIC AND ANATOMIC DETERMINANTS OF CORONARY BLOOD FLOW AND THEIR RELATIONSHIP TO MYOCARDIAL REVASCULARIZATION

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DISEASE of the coronary arteries resulting in myocardial ischemia continues to represent one of the most significant problems in medicine. Much effort is being directed toward a more fundamental understanding of this condition, particularly in association with the pathogenesis of atherosclerosis. In numerous studies attempts are being made to control the progression of the disease by the use of special diets, hormones, and a variety of drugs. Other investigators have directed their attention toward the *surgical* relief of myocardial ischemia. It is this aspect of the problem with its associated physiologic and anatomic features which will be considered primarily in this communication. Most of the data represent the results of studies performed in our own experimental laboratory or in those of others.

In any discussion concerning the coronary circulation it is essential to consider certain fundamental physiologic principles. The origin of the correct interpretation of the coronary circulation began with William Harvey in the seventeenth century, and since that time numerous contributions have been made describing the anatomic vascular channels of the heart. Much remains to be done in this important field. Many aspects of this problem, particularly in the human heart, remain unsolved.

The arterial supply of the heart arises from the two coronary arteries which are the first 2 branches of the aorta. After division these vessels eventually connect with a capillary bed which drains into the coronary venous circuit. The venous return of the heart empties largely into the right atrium through the coronary sinus. A significant amount of blood, however, returns through veins emptying directly into the right atrium. In addition to these channels there are other alternate pathways through which the blood may empty into either atrium

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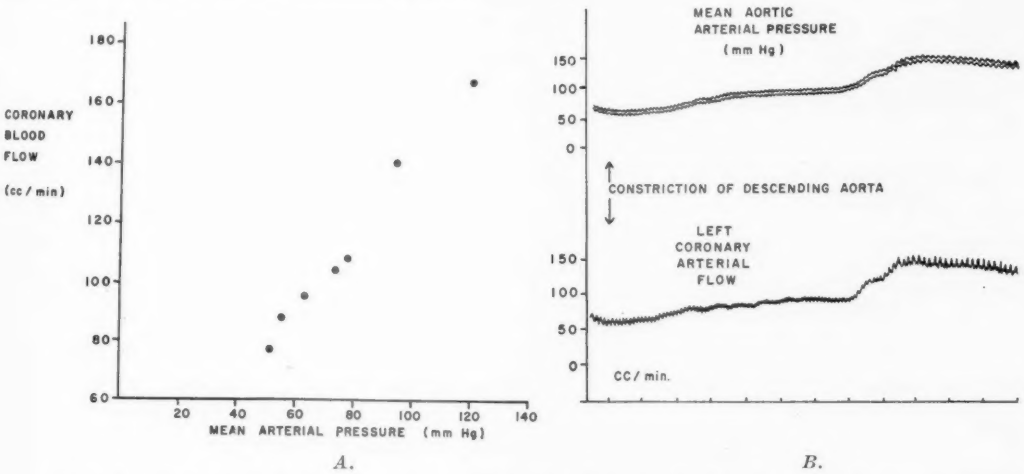
*Investigator, Howard Hughes Medical Institute.

or ventricle. The arterioles as well as the capillaries and superficial veins connect directly with both ventricular cavities by discrete deep drainage channels. The Thebesian vessels are known to drain venous blood directly into the ventricles.

In addition to the complex anatomic aspects of the coronary vascular system, there are numerous physiologic variables which are also determinants of coronary blood flow. These factors include: (1) the mean arterial pressure existing in the aorta which acts as the source of perfusion pressure for the coronary circulation, (2) the mean bore of the coronary vessels themselves (including pathologic obstruction), (3) the degree and duration of ventricular contraction, (4) the intrinsic vasomotor status of the coronary vessels, (5) the oxygen tension of the arterial blood, (6) the viscosity of the blood (affected by temperature and hemoglobin concentration), and (7) the venous pressure within the right atrium. Each of these variables exerts a varying degree of influence upon the quantity of blood flowing through the myocardial vascular bed, and under certain circumstances one or more of these factors may become much more prominent than in the normal physiologic state.



A. *B.*

Fig. 1.—*A*, Record illustrating the relationship of coronary blood flow and mean arterial pressure. Flow was determined in the left main coronary artery by direct cannulation and measurement with a rotameter and mean arterial pressure was recorded by a strain gauge. Alterations in the perfusion pressure were produced by constriction of the descending aorta. *B*, Graph illustrating pressure-flow pattern in the coronary arterial system. The points plotted were obtained from the record shown in *A*.

I. DETERMINANTS OF CORONARY FLOW

Coronary Arterial Pressure.—Coronary blood flow usually varies directly with the existing mean pressure within the coronary arterial system. There are exceptions, however, and the exact relationship of flow to central coronary pressure has been only partially elucidated.[16] In the experimental laboratory it can be demonstrated that an increase in the perfusing pressure within a coronary artery results in a corresponding increase in flow. An example of the effect of central coronary arterial pressure on the flow is shown in Fig. 1. With an increase in the central coronary pressure (produced by constriction of the descending aorta) there is a corresponding increase in the coronary flow. As the mean

arterial pressure is raised from 50 to 120 mm. Hg, the flow in the left coronary artery increases from 76 to 176 c.c. per minute. This pattern of flow response is one usually observed for mean arterial pressures within the physiologic range, although exceptions have been noted and discussed.[16]

The question arises as to the feasibility of increasing coronary flow by raising the pressure in the proximal aorta. In an experimental study, coaretation of the ascending aorta has been produced just above the orifices of the coronary vessels.[12] This places the coronary arteries under a marked hypertension with systolic pressures up to 300 mm. Hg while the remainder of the systemic circulation is perfused at an essentially normal pressure. After a period of observation the hearts of the animals were injected to demonstrate the vascular system. There was no evidence of a significant increase in the number of intercoronary collateral communications as compared with control preparations. It is recognized that such a constriction places an additional burden on the heart, and in any such procedure the resulting increase in cardiac work would very likely offset the advantage of increased coronary flow. It is interesting, however, that a chronically elevated perfusion pressure applied to the entire coronary circulation does not appear to produce a demonstrable increase in intercoronary communications.

The Effect of Lumen Size.—Although it might appear that the reduction in the diameter of the lumen would result in a corresponding decrease in flow through the vessel, this is not necessarily true. In mechanical systems with a high peripheral resistance, Gregg[16] has shown that a relatively large reduction in luminal area of the constricting tube is necessary to induce a significant reduction in the flow of the system. This factor is obviously an important one in regard to the pathologic lesions associated with atherosclerosis. It remains a fact, however, that reduction of the vessel diameter usually results in a reduction in flow. This principle is governed by Poiseuille's law which states that the rate of flow through tubes is directly proportional to the fourth power of the radius of the lumen and to the pressure differential between the two ends, and is inversely proportional to the fluid viscosity and to the length of the tube. There is little doubt that the obstructions resulting from coronary atheroma constitute the most important problem in the reduction of coronary flow. Although it is quite likely that minor degrees of reduction of the lumen by this process do not significantly alter flow, there is no doubt that progression of the disease has a serious effect upon the volume of coronary flow.

Effect of Ventricular Contraction.—The effect of organized cardiac contraction on blood flow through the capillary bed of the heart has long been a debated problem among physiologists. Evidence has accumulated to support the concept that the ventricular contraction acts as a "throttling" mechanism with a reduction in coronary flow.[30] This effect of cardiac contraction on coronary blood flow may be demonstrated in the laboratory by the perfusion of the heart from a reservoir of arterial blood maintained at constant pressure (equal to that of the prevailing mean aortic pressure). The coronary blood flow may then be recorded during a period of asystole and the volume compared with that

found in the beating heart perfused at the same pressure. During asystole the cardiac contraction is obviously eliminated, and the flow is measured during a prolonged period of diastole. Under these circumstances the blood flow invariably rises. A record from such an experiment is shown in Fig. 2. Coronary arterial flow in the control state is 119 c.c. per minute with an aortic perfusion pressure of 130 mm. Hg. With perfusion from the reservoir at a perfusion pressure of 119 mm. Hg, the coronary flow rises to 170 c.c. per minute during asystole (produced by vagal stimulation). A similar increase in flow is observed when the heart is perfused during ventricular fibrillation.[29] In other studies it has been shown that when the left coronary artery is perfused during systole at a pressure approximately equal to the prevailing mean aortic pressure, arterial inflow approaches zero.[17] Although it is obvious that cardiac contraction is necessary in order to produce a pressure within the aorta, it is also apparent that the effect of contraction per se is to reduce the amount of blood flowing through the heart during the period that the heart is in the contracted state.

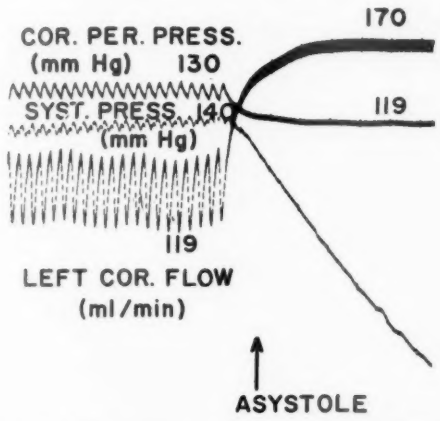


Fig. 2.—Record illustrating the effect of cardiac contraction on coronary blood flow. Flow is determined by direct cannulation of the left main coronary artery attached to a rotameter and a constant pressure reservoir of arterial blood. Control mean flow in the left coronary artery is 119 ml. per minute with a perfusion pressure of 130 mm. Hg (from the constant pressure reservoir). With the induction of asystole by vagal stimulation and continued coronary arterial perfusion at 119 mm. Hg coronary arterial flow rises precipitously to 170 ml. per minute.

This fact has led to a consideration of the creation of a delay in the systolic peak of the blood supply to the coronary arteries by means of a long graft placed between the aorta and the coronary arteries. Under these circumstances the myocardial vascular bed is perfused with a peak pressure occurring during the period in which the heart is in a state of diastole. Experimental studies have suggested that it is possible to augment coronary flow by this method.[21] For a variety of technical reasons the procedure does not appear to be a feasible one at present. Nevertheless, the underlying principles involved are sound.

The Effect of Oxygen Tension in the Arterial Blood.—The prevailing oxygen tension in the blood entering the coronary vessels exerts a marked effect upon the volume of blood flow through the myocardial vascular bed. Anoxia is known to be a powerful coronary vasodilator. An illustration of the effect of arterial oxygen saturation on coronary blood flow is shown in Fig. 3. The control flow in the

circumflex coronary artery is shown at 21 c.c. per minute with a perfusion pressure in the aorta of 100 mm. Hg. Asystole is induced, and the flow in the coronary artery rises to 55 c.c. per minute (perfusion with fully saturated blood from a reservoir at a pressure of 100 mm. Hg). When the blood in the reservoir is changed from that of 100 per cent saturation to a saturation of 6 per cent, the flow in the circumflex coronary artery rises to 77 c.c. per minute in the beating heart. This represents a marked increase in flow and is due to the change in oxygen saturation inasmuch as the perfusion pressure remains constant. When asystole is introduced, the flow rises to 105 c.c. per minute. With escape from asystole and return to the beating heart, the control flow is 96 c.c. per minute after 70 seconds of perfusion of blood of 6 per cent oxygen saturation. The introduction of asystole at this point results in a flow of 109 c.c. per minute.

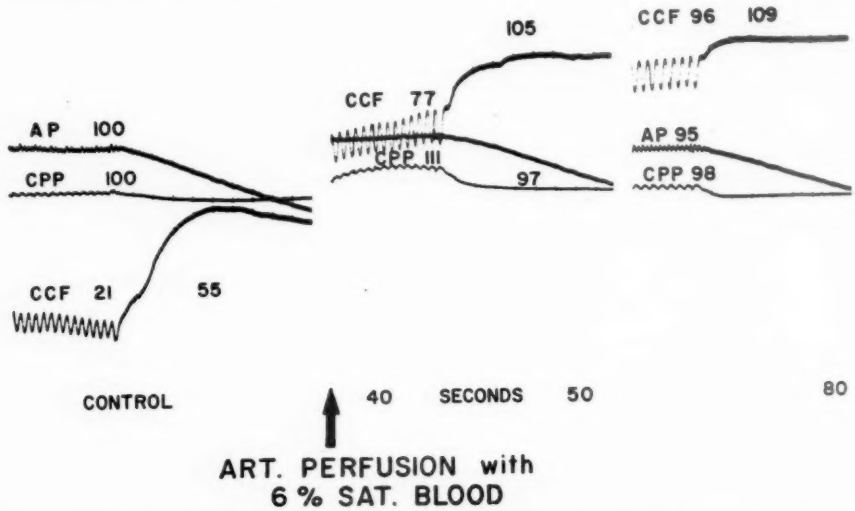


Fig. 3.—Illustration of effect of arterial oxygen saturation on coronary blood flow. The circumflex coronary artery is cannulated and perfused from a constant pressure reservoir of blood. In the control state the flow is 21 ml. per minute at a perfusion pressure of 100 mm. Hg. With the onset of asystole the flow rises to 55 ml. per minute. At this point the heart resumes a normal beat and the blood in the reservoir is changed from 100 per cent saturation to 6 per cent saturation (marked by arrow). The circumflex coronary flow then quickly rises to 77 c.c. per minute at a perfusion pressure of 111 mm. Hg. With the onset of asystole the flow rises to 105 ml. per minute. One minute following the onset of coronary arterial perfusion with blood of 6 per cent oxygen saturation the mean circumflex coronary flow in the beating heart is 96 ml. per minute and with the induction of asystole there is a slight further rise to 109 ml. per minute. Further determinations (not shown) were performed with no further increase in coronary flow in the beating heart or in asystole. At this point it appeared that the dilatation of the coronary arterial bed was near a maximum. (AP, aortic pressure; CPP, coronary perfusion pressure; CCF, circumflex coronary flow.)

It can be seen that the control flows in the beating heart and the flow during asystole approach each other as the coronary bed becomes maximally dilated in response to the marked anoxia. In fact, subsequent determinations on the same preparation (not shown in the illustration) demonstrated that no further increase in flow could be obtained. In other words, the coronary vascular bed appeared to be maximally dilated. This physiologic vasodilatation of the coronary bed in response to anoxia has been thought to be the most effective means of developing a collateral circulation in the ischemic heart. Many are of the opinion that this mechanism is the chief one which supplies collateral circulation to an infarcted area following coronary arterial occlusion and is ultimately responsible for recovery in those who survive.

The Effects of Viscosity and Temperature.—In a mechanical system, flow is inversely proportional to the viscosity of the perfusate. Under most physiologic conditions the viscosity of the blood remains within narrow limits. Marked anemia may decrease the viscosity, and under these circumstances coronary blood flow has been shown to be increased.[9] However, anemia is also associated with a reduction in the oxygen capacity of the blood and produces vasodilatation resulting in greater flow. Temperature is also an important factor in the determination of viscosity. For example, the viscosity of the blood may be increased two- or threefold by lowering the temperature of the body to 25° C., and this may be of significance in patients undergoing hypothermia. Experimental studies have shown that coronary blood flow at the temperature generally employed in clinical hypothermia is probably adequate.[31] Under these circumstances cardiac work is reduced with a decrease in cardiac rate, mean arterial pressure, and cardiac output. Coronary blood flow has been found to constitute a greater percentage of the cardiac output at a body temperature of 25° C. than at the normal temperature of 37° C. Such data suggest that the heart appears to be selectively favored during hypothermia.

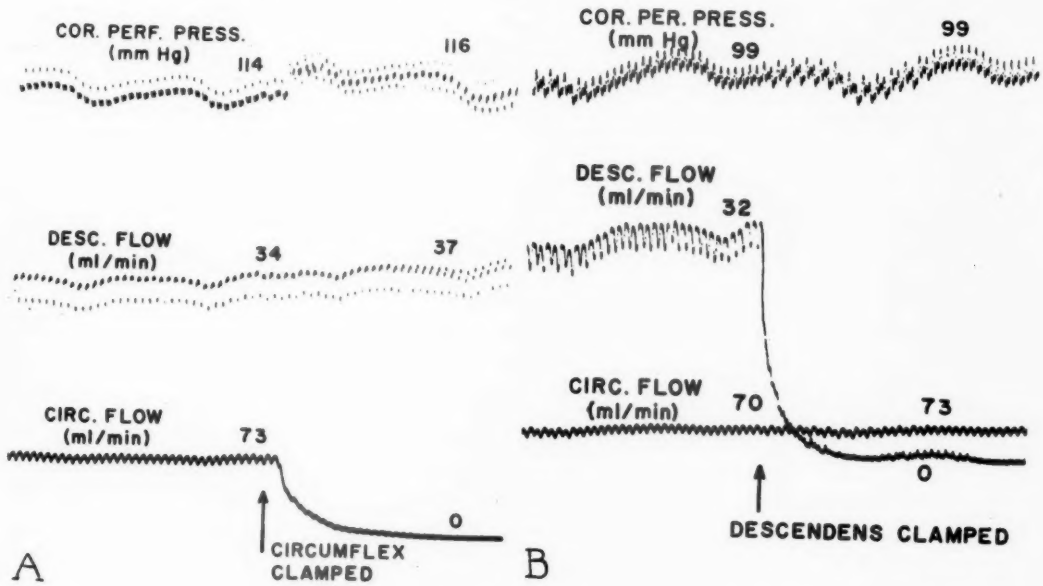


Fig. 4.—*A*, Illustration of record obtained during measurement of circumflex and anterior descending coronary arterial flow by rotameter. The control flow in the circumflex artery is 73 ml. per minute and that in the anterior descending is 34 ml. per minute at a perfusion pressure of 114 mm. Hg. With occlusion of the circumflex artery the flow in the anterior descending is only minimally increased, if at all. *B*, Illustration of record of coronary blood flow in the anterior descending and circumflex coronary arteries. Control flow in the anterior descending artery is 32 ml. per minute (mean aortic pressure of 99 mm. Hg). With occlusion of the anterior descending, blood flow in this vessel falls to zero with only a minute rise in the circumflex flow to 73 ml. per minute. (Coronary perfusion pressure remains at 99 mm. Hg.)

Presence of Intercoronary Collateral Vessels.—The presence of sizable intercoronary communications in both man and the dog have been demonstrated in the normal heart. However, such communications (of 100 micra and larger) are unusual and occur in only 9 per cent of human beings and in a slightly higher percentage of dogs.[7, 37] The physiologic importance of this lack of communication

may be demonstrated by simultaneous measurement of flow in the anterior descending and circumflex branches of the left coronary artery. The data from such an experiment are shown in Fig. 4, *A*. With continuous measurement of flow in the anterior descending coronary artery, the control flow is 34 c.c. per minute and in the circumflex coronary artery 73 c.c. per minute. With occlusion of the circumflex artery, the flow in this vessel diminishes to zero. However, there is very little increase in the flow in the anterior descending coronary artery during this period. In fact, the flow only rises to 37 c.c. per minute, and during this time there is an associated slight increase in the coronary perfusion pressure (114 to 116 mm. Hg) which might account for the slight rise in flow. In other words, the experiment demonstrates that there is very little if any increase in anterior descending flow following occlusion of the circumflex coronary artery. Similar findings are shown in an experiment with occlusion of the anterior descending coronary artery (Fig. 4, *B*).

II. EXPERIMENTAL MYOCARDIAL REVASCULARIZATION

For many years efforts have been made to increase the blood supply to the myocardium by various surgical means. Most of the procedures employed fall into one or more of the following groups: (1) the introduction of an irritant into the pericardial cavity, (2) the grafting of other organs or tissues to the surface of the heart, (3) the anastomosis of a systemic artery to the coronary sinus, (4) the implantation of a systemic artery into the left ventricular myocardium, (5) direct anastomosis of a systemic vessel to a coronary artery, (6) coronary endarterectomy, and (7) ligation of the internal mammary artery. In our laboratory some of these approaches have been explored, and an attempt has been made to evaluate them.

One of the most difficult problems encountered in studies on myocardial revascularization is an accurate and objective measurement of the results. The most commonly employed test of an operation designed to "protect" the heart is that of occlusion of one of the major coronary arteries. Customarily the anterior descending coronary artery has been ligated with a subsequent study of the immediate mortality, and in the survivors the extent of myocardial infarction is determined. Although there is a difference of opinion concerning the percentage of normal animals which succumb to anterior descending coronary artery ligation, the majority of those interested in the subject have found that the mortality approximates 70 per cent.[4, 6, 8, 10, 11, 15, 18, 19, 33] Chardack and associates[10] have reported the lowest mortality following this procedure and found that only 10 per cent of the animals died. Their studies are not strictly comparable to those of others since oxygen was used during the procedure. There is little question that the exact site of ligation of the anterior descending coronary artery and certain anatomic variations which may occur are of prime importance in determining the results. For example, the anterior descending artery should be ligated exactly at its origin from the left main coronary artery if the test is to be a standard one. The only exception to this rule occurs in those instances in which the septal branch originates from the anterior descending, and in such animals all branches of the anterior descending artery arising above

the origin of the septal branch must be ligated and the anterior descending artery itself ligated immediately distal to the origin of the septal branch. In the majority of instances the septal artery originates posteriorly or medially as a separate branch of the left main coronary artery. There is also little doubt that in those instances in which a large branch arises from the circumflex near its origin (following the normal anterior descending coronary artery as an accessory vessel) the percentage of survivors is greater. However, in the performance of the procedure in a number of animals, one is unlikely to encounter an unusually high percentage of such anatomic variations. The pattern of the left coronary artery and its branches should be recorded and borne in mind in the evaluation of results following ligation. In our own laboratory, using the criteria previously mentioned, the mortality of ligation of the anterior descending coronary artery in the dog is 70 per cent.[28] In the survivors the area of infarction usually involved most of the anterior wall of the left ventricle and the left border of the right ventricle (Fig. 5, *A*).

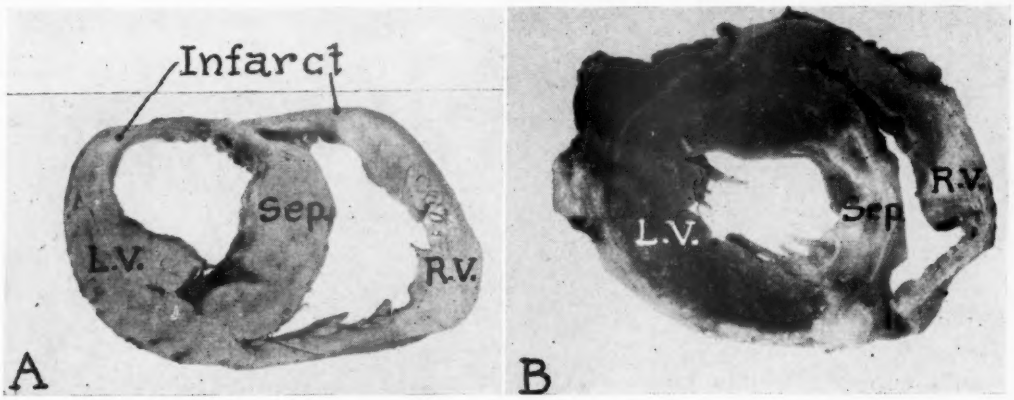


Fig. 5.—*A*, Photograph of transverse section of the heart taken through the mid-portion of both ventricles. The anterior descending coronary artery was ligated at its origin 2 months previously with recovery of the animal. A large infarct is present in the anterior left ventricle extending across the septum to involve the medial portion of the anterior wall of the right ventricle. *B*, Section of heart taken through the mid-portion of both ventricles in an animal previously subjected to de-epicardization (phenol), cardiomediastinopexy, and asbestos poudrage. Three months following operation the anterior descending coronary artery was ligated at its origin. The animal was sacrificed 2 months subsequently without gross evidence of myocardial infarction. On examination the anterior left ventricle appears normal.

Another method frequently employed to assess the value of a procedure designed to determine an increase in myocardial blood supply is that described by Mautz and Gregg.[25] By ligation of either the circumflex or anterior descending coronary arteries and cannulation of the distal end of the vessel, it is possible to measure quantitatively the backflow. It has been shown that this backflow consists of blood with an oxygen saturation of that of arterial blood and is an index of the number and size of intercoronary communications. Significant increases in backflow are usually well correlated with increases in intercoronary collaterals as demonstrated by injection techniques.

A. De-epicardization, Cardiopexy, and Poudrage.—The concept of the stimulation of the development of intercoronary collateral vessels by surgical methods should be attributed largely to Beck.[6] He has done a variety of studies

on this problem and is convinced that the Beck I operation (de-epicardization, asbestos poudrage, cardiomediastopexy, and partial ligation of the coronary sinus) produces a balanced arterial circulation in the heart. He has advanced the concept that it is the differential in oxygenation tension within adjacent areas of the ventricular myocardium which is responsible for acute ventricular fibrillation in association with acute infarction. It is his opinion that following operation blood is shunted from a portion of the coronary circulation which is well supplied to a portion which is less well supplied with much reduction in the danger of fatal arrhythmia. In a number of experimental studies he has shown that intercoronary collaterals are increased as demonstrated by a rise in backflow measured by the Mautz-Gregg technique.[25]

In our laboratory a group of animals were subjected to a chemical de-epicardization (by the use of concentrated phenol), a cardiopneumopexy, and asbestos poudrage. Following a period of observation the anterior descending coronary artery was ligated. In this group 80 per cent of the animals survived and in the hearts examined at the time of sacrifice there was rarely evidence of gross myocardial infarction (Fig. 5, *B*). Microsopic scarring, however, was present in the tissue sections.

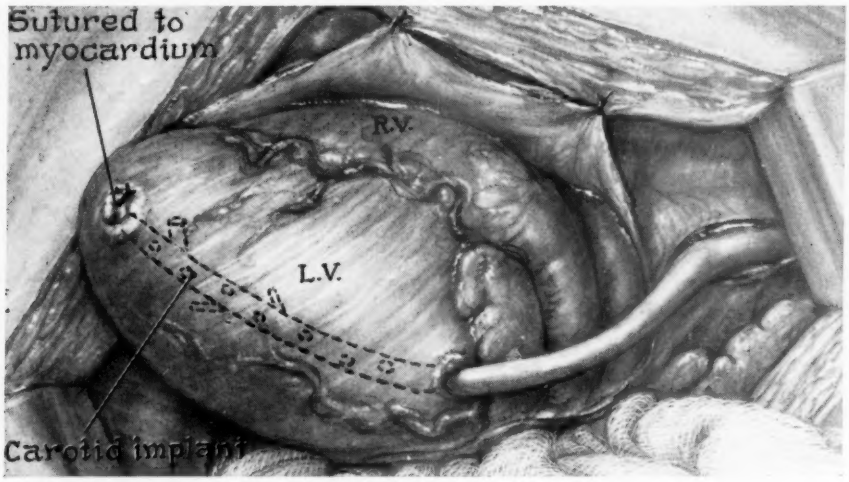


Fig. 6.—Illustration of technique employed in the implantation of the left carotid artery into an intramyocardial tunnel of the left ventricle.

B. Implantation of a Systemic Artery Into the Myocardium.—In 1946 Vineberg[35] first demonstrated the development of anastomotic communications between an internal mammary artery implanted into the left ventricle and the coronary circulation. He and his associates[36] have continued their investigations and have accumulated a number of patients with coronary arterial insufficiency in whom this procedure has been performed. As a result of experimental and clinical studies, it is their belief that the internal mammary artery remains patent in the majority of cases and conducts a significant amount of blood to the myocardium. Other investigators have employed the internal mammary artery in experimental studies and have reported conflicting results.[3, 13, 14, 24]

We have conducted studies on this problem but have elected to use a larger vessel than the internal mammary and have chosen to implant the carotid artery in a long tunnel in the left ventricle (Fig. 6). Subsequent studies on these animals have shown that approximately 90 per cent of these implants remain patent (Fig. 7, *B*). Radiopaque material injected into the carotid implant demonstrated filling of the normal coronary arterial system in 82 per cent of the specimens (Fig. 7, *A*). Somewhat disappointing, however, was the fact that only small volumes of blood could be shown by direct measurement to flow from the implant into the myocardium in the majority of the hearts.[28] In further studies designed to quantitate the volume of arterial blood entering the heart through the implant, it was found that measurement of total coronary sinus flow is not appreciably altered by temporary occlusion of the carotid implant (Fig. 8). Definite protection could be shown, however, against ligation of the anterior descending coronary artery. The survival rate in the experimental group was 64 per cent as compared with 30 per cent in controls. The microscopic changes in the carotid artery were interesting and occurred in the majority of the implants. The intimal layer was thickened, particularly near

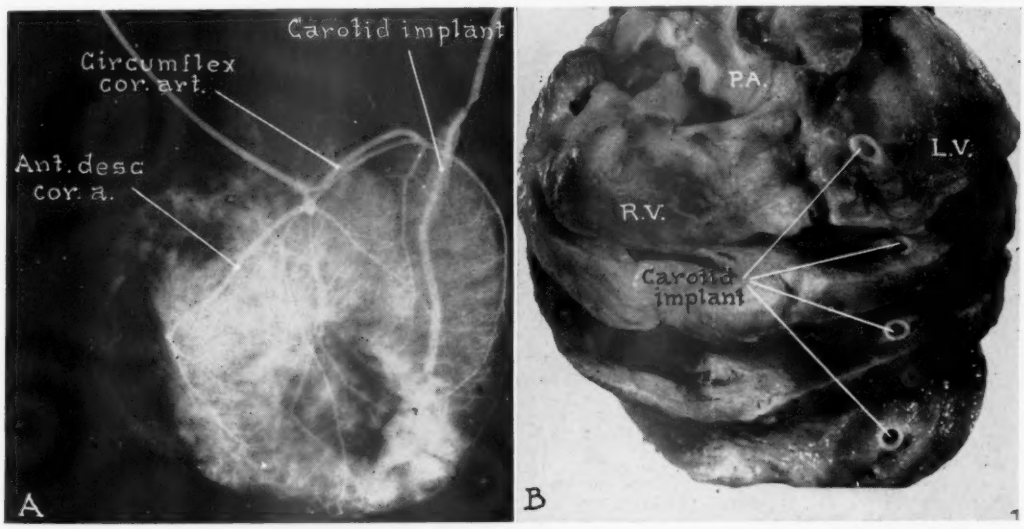


Fig. 7.—*A*, Photograph of film showing injection of carotid implant with sodium iodide 18 months after implantation. The coronary arterial system of the left ventricle is well filled and the anterior descending and circumflex coronary arteries are demonstrated. *B*, Gross specimen of heart shown in *A*. The carotid implant remains patent from the base of the left ventricle to the apex.

the distal end of the implant, and this change appeared to be the result of fibrous organization of thrombus on the vessel wall. In an associated study implants of systemic arteries (carotid, femoral, and renal) into organs other than the heart (liver, spleen, and sternomastoid muscle) resulted in complete thrombosis in nearly all the preparations.[28] Similar implants into the wall of the right ventricle showed a somewhat lower incidence of continued patency of the vessel under these circumstances.[27] The carotid remained patent in approximately two-thirds of the animals with thrombotic occlusion in the remainder. Vascular communications could be demonstrated between the patent

implant and the coronary arterial system, although the volume of flow was quite small. There did appear to be definite difference in the response of arterial implants in the right ventricle as compared with similar ones in the left ventricle. It was thought that the diminished contractile force in the wall of the right ventricle might be responsible for this difference.

C. Direct Systemic-Coronary Artery Anastomosis.—Pathologists have shown that the major changes occurring in coronary atherosclerosis are largely confined to the larger arteries. Most observers agree that coronary atherosclerosis is not a disease of the small intramyocardial arteries but is most frequently found in the larger subepicardial vessels. In fact the disease is often localized to the first 4 cm. of the coronary vessels.[32] For this reason the possibility of making a direct anastomosis of a systemic artery to the coronary artery distal to the site of occlusion has been considered. The plan may be a feasible one

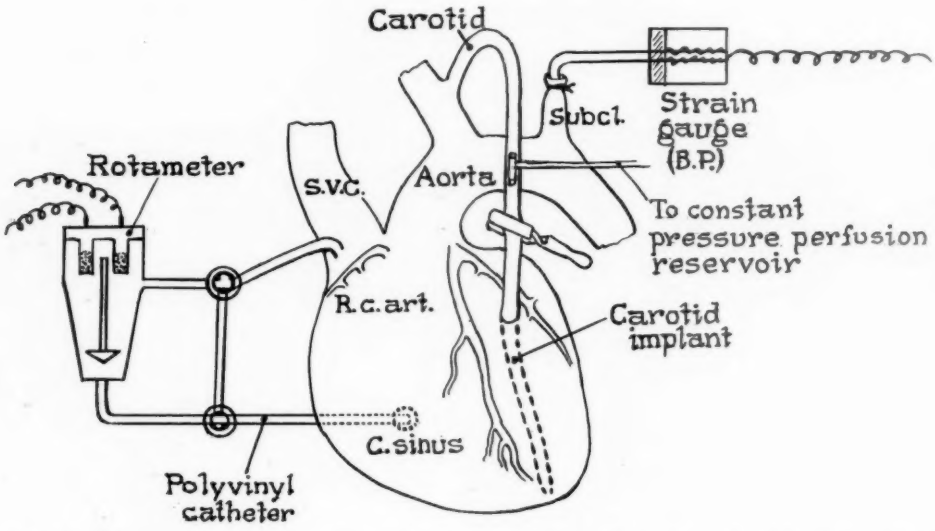


Fig. 8.—Diagrammatic illustration of technique employed to determine blood flow through the carotid implant. The cannula in the implant is connected to a constant pressure perfusion reservoir filled with arterial blood. With temporary occlusion of the implant proximal to the cannula, blood flow through the implant into the heart may be determined. A polyvinyl catheter is sutured into the coronary sinus in order that total coronary sinus flow may be measured by the rotameter during alternate occlusion and patency of the carotid implant.

from the technical viewpoint and it is possible, for example, to perform a successful anastomosis between the subclavian artery and the end of the circumflex or anterior descending coronary arteries. In our laboratory this procedure was performed in a number of animals by autoperfusion of the distal end of the coronary artery by a shunt. A polyethylene catheter was placed into the subclavian and drawn out its distal end and passed into the end of the circumflex coronary artery. An anastomosis was performed over the catheter while the coronary artery was constantly being perfused. At the conclusion of the anastomosis the polyethylene catheter was withdrawn. An illustration of an anastomosis done by this method is shown in Fig. 9. In this animal the anastomosis was performed between the end of the subclavian artery and the end of the circumflex coronary artery. The animal survived and was sacrificed 5

months after operation, at which time the anastomosis was found to be patent and the heart otherwise normal. This specimen does not represent, however, the usual result of such a procedure. The immediate mortality of the operation is high and some of the survivors ultimately succumb as a result of thrombosis occurring at the site of the anastomosis. Such a thrombus is seen just distal to the anastomosis in Fig. 10. The size of the coronary vessels is undoubtedly a considerable factor in the ability of the vessels to remain patent following vascular anastomosis. The anastomosis of vessels of small caliber in various regions of the body has led to thrombosis in many instances, and it is quite probable that the coronary circuit will not prove to be an exception. Despite this, interest continues in this method of attack, at least in the experimental laboratory, and Thal and associates[34] have reported a commendable study with this technique and mention the possibilities of clinical application.

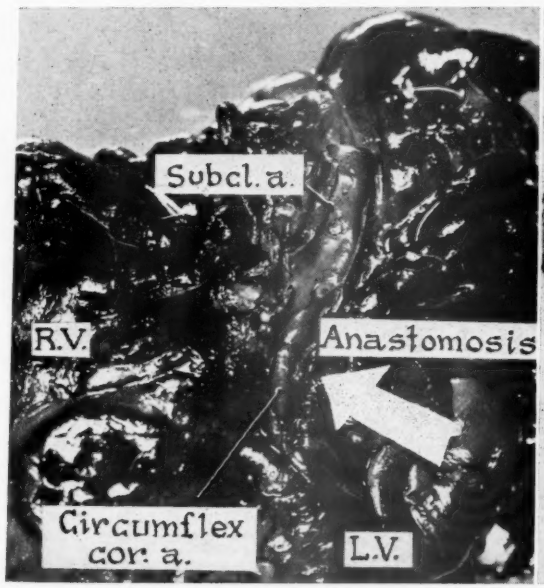


Fig. 9.

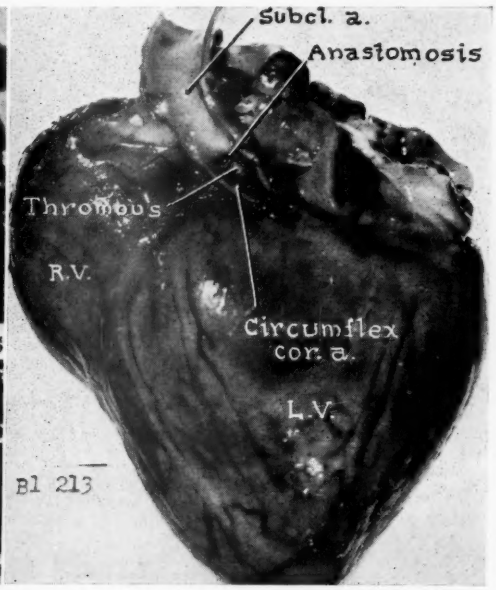


Fig. 10.

Fig. 9.—Photograph of heart showing anastomosis (arrow) of the end of the subclavian artery to the end of the circumflex coronary artery. The animal was sacrificed after 5 months and the anastomosis was patent. The remainder of the heart was normal.

Fig. 10.—Photograph of heart showing anastomosis of the end of the subclavian artery to the end of the circumflex coronary artery. The animal died on the tenth day following operation and a thrombus was found at the anastomotic site.

D. Ligation of the Internal Mammary Artery.—During the past several years there has been considerable discussion concerning the clinical use of ligation of the internal mammary artery in the management of myocardial arterial insufficiency. It is maintained that the basis for internal mammary artery ligation is found in anatomic studies which demonstrate communications between the branches of the internal mammary artery and the coronary circulation. A number of observations has been made confirming the fact that there are small channels which link these circulations, and the pericardiophrenic branch of the internal mammary is one of the principal vessels in this collateral path. In 1880 Langer[22] described branches of the coronary arteries which anastomose with

vessels of the mediastinum, diaphragm, parietal pericardium, and hila of the lungs. Wearn[20] demonstrated that following injection of the coronary arteries by India ink small vessels along the ascending aorta were also filled. Other studies have shown widespread anastomoses of the atrial arterial branches with the pericardial fat. Stimulated by the knowledge of these anatomic communications, Battezzati, Tagliaferro, and DeMarchi[5] have advocated internal mammary artery ligation for coronary insufficiency. They have performed this procedure in a large number of patients and appear to be gratified with the results. Glover and associates[15] have also applied this procedure extensively and recommend it.

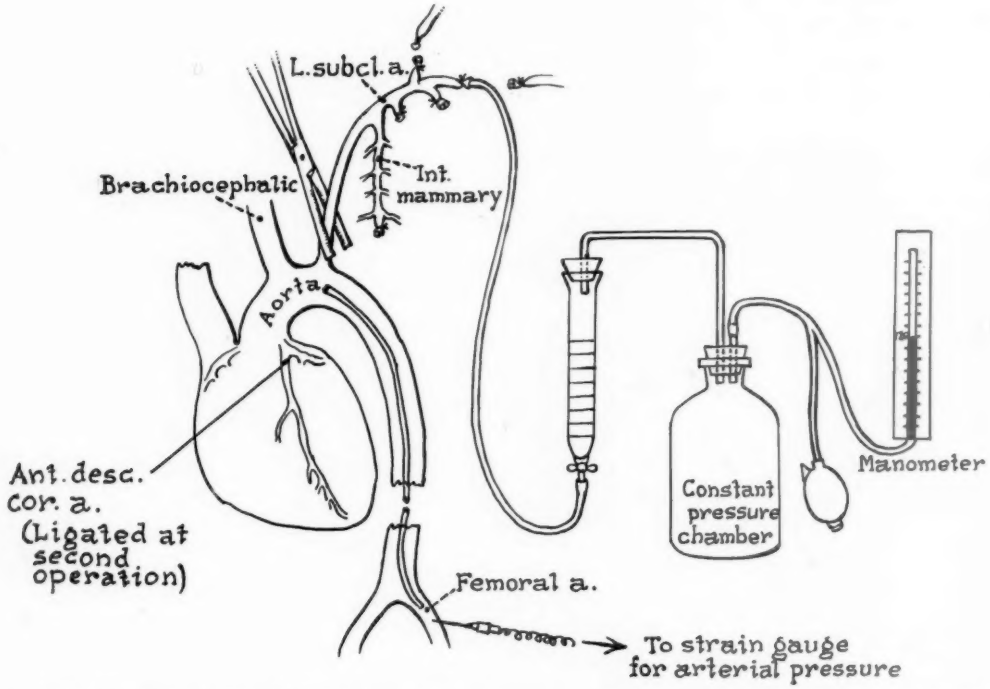


Fig. 11.—Diagrammatic illustration of technique employed in determination of blood flow in the internal mammary artery. With temporary occlusion of the subclavian artery at its origin, blood may be perfused from the burette at a constant pressure (equal to the prevailing mean aortic pressure) with measurement of internal mammary arterial flow. The anterior descending coronary artery was ligated at a subsequent operation as described in the text.

In a group of experimental studies performed in our laboratory, an attempt was made to measure the volume of blood flow through the internal mammary artery after its ligation in the second intercostal space.[26] An effort was made to determine the effect of time on the volume of this flow subsequent to ligation. Three groups of animals were studied. In the first group the internal mammary artery was ligated in the second intercostal space, and blood flow was determined immediately in this vessel by a direct technique. One of the branches of the subclavian artery was cannulated and attached to a graduated burette such that blood could flow into the burette and then be perfused into the internal mammary at the prevailing mean aortic pressure (Fig. 11). During the time that the measurement was recorded the subclavian artery was temporarily occluded. Under these circumstances all the blood flow entering the subclavian artery from the constant pressure reservoir could make its exit only through the

branches of the internal mammary above the point of ligature of that vessel. The data showed that the average flow through the internal mammary at the prevailing aortic pressure was 2.7 c.c. per minute. In a similar group of animals the blood flow was determined 6 weeks following ligation of the internal mammary artery. Little change was noted and the average flow was found to be 2.9 c.c. per minute. There was also very little difference in the measured back pressure in the internal mammary. In the first group the back pressure was 43 mm. Hg and in the second group the back pressure was 48 mm. Hg. Similarly, the backflow from the internal mammary was quite low in both instances. In the first group it was found to be 0.5 c.c. per minute and in the second group 0.8 c.c. per minute. In other words, there was no indication that an increase occurred in flow, backflow, or back pressure with the passage of time. In a third group of animals all branches of the subclavian artery were ligated and the internal mammary artery was ligated in the second intercostal space. The animals were then observed for a period of approximately 6 weeks, and flow and pressure studies were again determined. It was interesting that the flow under these circumstances was much greater and averaged 10 c.c. per minute. The measured back pressure was appreciably higher than that of the other groups and was found to average 73 mm. Hg. The backflow was also increased and measured 9.5 c.c. per minute. Under the conditions of the experiment in this third group, a considerable stimulus for the development of collateral circulation was established, and it was possible to produce marked augmentation in both pressure and flow.

In the three groups in which the internal mammary arteries were ligated, each was tested against ligation of the anterior descending coronary artery. It was not possible to demonstrate protection in any of the three groups. In all instances the mortality following anterior descending ligation was either the same or greater than similar figures for ligation in the control state. This indicated that even under circumstances of increased flow in the internal mammary artery an insufficient amount of this flow reached the heart to produce any demonstrable protection against coronary occlusion.

E. Direct Coronary Endarterectomy.—Since coronary atherosclerosis usually occurs in the proximal portions of the coronary arteries, the direct removal of these occluding lesions presents an interesting challenge. Bailey and associates[2] have employed this method clinically and others[1] have reported similar pathologic studies. The concept of the direct removal of the occluding lesions is a fascinating one, and comparisons may be made between the coronary arteries and other arteries with occluding lesions which have been removed successfully. Again the size of the vessels and the relationship to subsequent thrombosis would appear to be of the greatest importance.

In a combined study with the Department of Pathology* during the past year we have examined the hearts of patients whose death was the result of myocardial infarction. The hearts are examined as soon after death as possible, and are immersed in a saline solution at 37° C. The left and

*Studies done in association with Dr. William M. Shelley of the Department of Pathology.

right coronary arteries are dissected, and small polyethylene cannulae are sutured in place. Diodrast is injected and an arteriogram is obtained. Saline is then perfused through the right and left coronary arteries at various pressures and pressure-flow curves are constructed. After study of the arteriogram, a direct arteriotomy is made at the site of the vascular obstruction. In the majority of the specimens the occlusion has been in the proximal portions of the coronary arteries, usually one of the branches of the left coronary artery (anterior descending or circumflex) (Fig. 12). It has been rather surprising to observe the ease with which the atheromata may be removed by the use of selected instruments. The remaining wall is usually thin and quite smooth. Following removal of the occluding lesion the longitudinal arteriotomy incision is closed with fine arterial silk, and the perfusion studies are repeated.

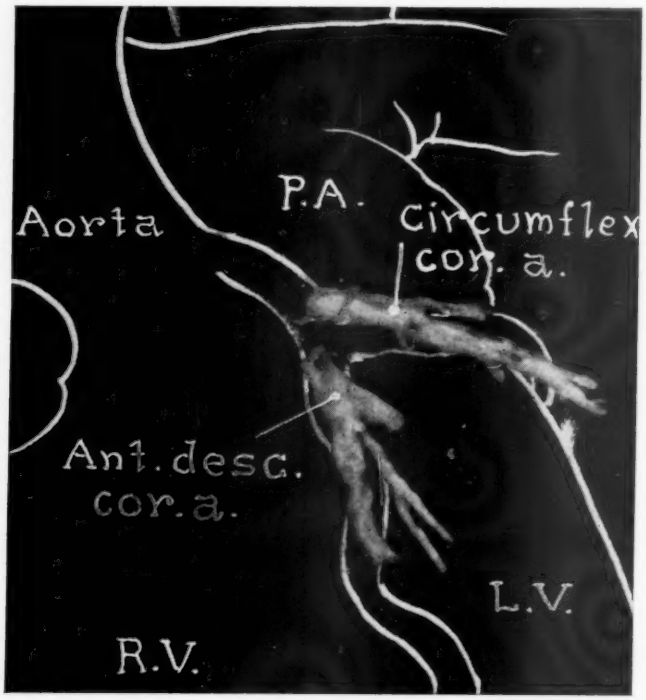


Fig. 12.—Diagram of human heart with superimposed atheromatous lesions removed from the circumflex and anterior descending coronary arteries at post-mortem examination.

With these techniques it has frequently been possible to demonstrate an increased flow following endarterectomy. Histologic sections have shown that the cleavage plane most often occurs in the muscular layer of the arterial wall and that the atherosclerotic process is primarily limited to the inner layer of the muscularis and the intima. An illustration of a proximal coronary artery with occluding thrombus is shown in histologic section in Fig. 13, *A*. The atheroma has been stripped from the wall and remains in situ. In Fig. 13, *B* a section taken through an occluding lesion removed from the vessel is shown. A tiny central lumen is present, and it is in such a lumen that recent thrombosis is often found. The histologic appearance of the artery following endarterectomy

is shown in Fig. 13, *C*. The section has been stained to demonstrate the elastic tissue (Verhoeff-van Gieson), and the internal and external elastic lamellae are easily seen.

The direct approach to the problem of coronary arterial occlusion is a particularly attractive one. Recently, Longmire and Cannon[23] have successfully employed this method in several patients and are encouraged by the early results. It is certain that this attack merits more study and should be pursued further.

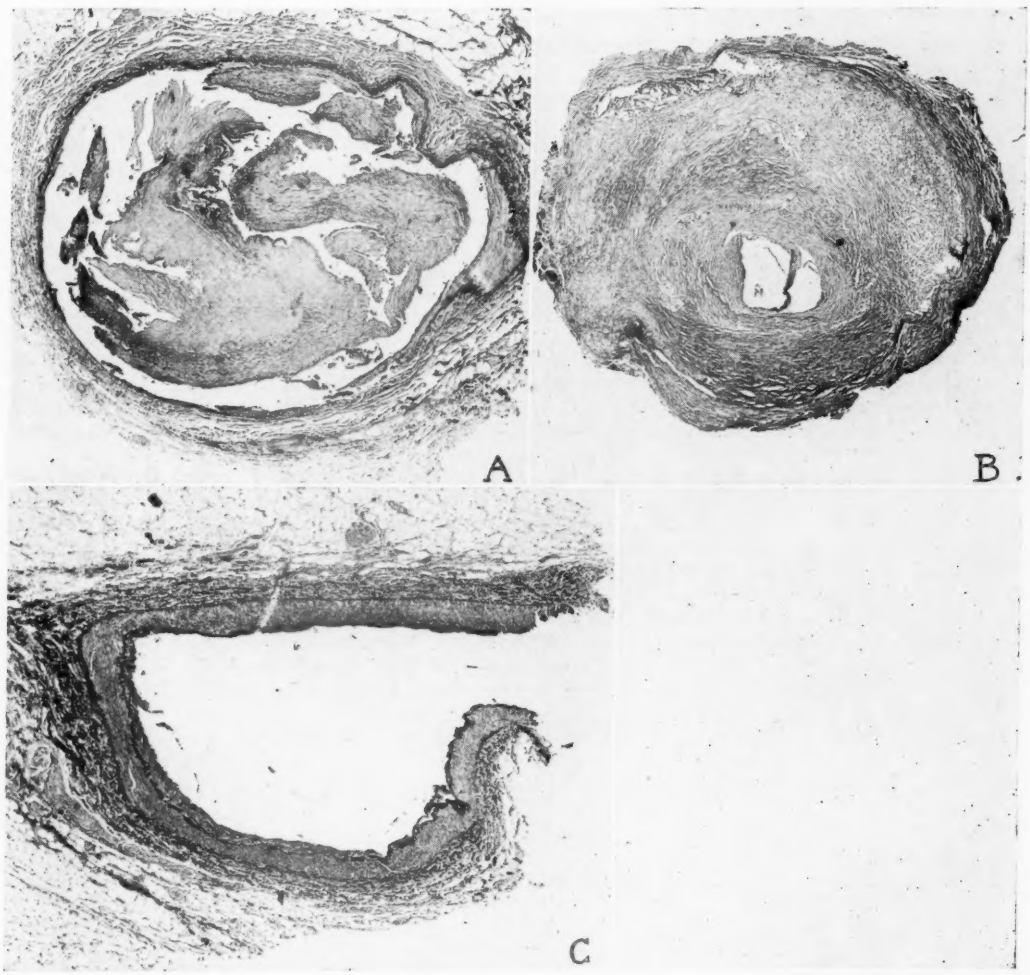


Fig. 13.—*A*, Photomicrograph of anterior descending coronary artery following dissection of occluding lesion from the arterial wall. The occluding lesion remains in situ. *B*, Photomicrograph of section of excised plaque from anterior descending coronary artery. A small central lumen is present. *C*. Photomicrograph of wall of anterior descending coronary artery following endarterectomy. The section is stained to demonstrate elastic tissue (Verhoeff-van Gieson). The internal and external elastic lamellae are well seen. The internal surface of the wall appears reasonably smooth.

SUMMARY

Some of the anatomic features and physiologic variables controlling flow through the coronary vascular bed are discussed. These factors are considered

with their relationship to various attempts to revascularize the heart. Experimental attempts directed toward increasing coronary blood flow by (1) an increase in intercoronary collateral vessels, (2) ingrowth of new vessels, and (3) direct removal of obstructing lesions are reviewed. There has been considerable recent progress in an improved understanding of the hemodynamics of the normal and diseased coronary circulation. The results of various experimental studies are sufficiently encouraging to warrant a continued attack on the problem by surgical means. Despite this, much remains to be done in an effort to produce an adequate degree of myocardial revascularization in the heart with extensive coronary arterial disease.

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Appraisal of Progress in Surgical Therapy

CONDUCTED BY WARREN H. COLE, M.D.

INTENSIVE PREOPERATIVE NUTRITIONAL THERAPY

JOHN H. SCHNEEWIND, M.D., CHICAGO, ILL.

(From the Department of Surgery, University of Illinois, College of Medicine)

NOT ALL surgeons are convinced that restoration of weight loss, at least partially, prior to operation is essential for malnourished surgical patients. Acute starvation, in addition to the underlying disease, represents a stress which invokes increased adrenal cortical activity and other endocrine reactions. The patient loses weight, uses liver and muscle protein for energy purposes instead of tissue repair, and goes into a negative nitrogen balance. Prolonged malnutrition may be associated with a gradual decrease in metabolic rate, decrease in body size and reduced hormone output by the pituitary, thyroid, and adrenal glands.[1] In time, atrophy of these glands may occur.

It rarely is possible to replace weight loss completely; however, by changing negative nitrogen balance to positive and achieving a 4 or 5 pound weight gain, it may be that just enough protein replacement for liver, pituitary, adrenal, and so forth is provided to favorably influence recovery.

Although the basic principles of good nutrition are well known, individual patients often require specific emphasis on certain aspects of rapid preoperative build-up. Examples of some of these problems and the therapy used are presented.

Use of Human Albumin in Correcting Marked Hypoproteinemia.—A 30-year-old white man was admitted because of chronic diarrhea and a 30-pound weight loss. For 5 years the patient had suffered periodic episodes of cramping abdominal pain, vomiting, and alternating obstipation and diarrhea. On examination the patient was severely malnourished, the abdomen was somewhat distended, and the bowel sounds were hyperactive. He weighed 102 pounds; the albumin-globulin ratio was 1.8 to 2.4; the hematocrit was 43. Soon after admission the patient was given 50 Gm. of human albumin intravenously daily. After he had received a total of 375 Gm., the hematocrit fell to 23. The initial hematocrit of 43 undoubtedly was misleading and reflected a significant reduction in blood volume. Transfusions totaling 4,000 c.c. of whole blood were required to bring the hematocrit back to normal. At this time the A/G ratio was 4.0 to 1.5. The patient was taken to the operating room where an ileotransverse colostomy

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was performed for a constricting regional ileitis; the terminal ileum was dilated and edematous. The patient did fairly well after operation. Despite 5 to 6 bowel movements daily and occasional cramps and distention, he gained 25 pounds in 6 weeks. At this time the A/G ratio was 4.7 to 2.8 and hematocrit was 39. Another celiotomy was performed at which time the previous ileocolostomy was taken down, the distal ileum was resected, and an ileocolostomy was done. Two and one half years later the patient weighed 132 pounds, was having 2 or 3 bowel movements daily, and felt very well. Barium study of the intestinal tract was read as normal.

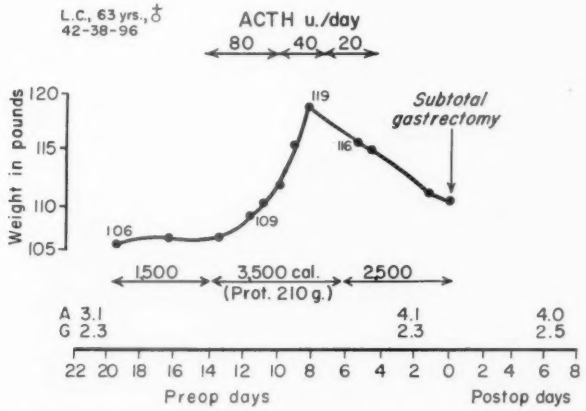


Fig. 1.—Caloric intake and body weight curve following administration of ACTH. This 63-year-old white woman had intermittent episodes of jaundice following cholecystectomy and had recently developed melena. There was an immediate improvement in appetite soon after ACTH was started. Although a part of the initial weight gain was due to water retention, her general nutrition was substantially improved prior to operation.

Use of ACTH to Increase Dietary Intake.—An example of the value of ACTH in promoting increased food intake in selected patients may be illustrated by the case of a 63-year-old white woman with a history of 6 previous admissions to the surgical service because of recurrent jaundice following cholecystectomy. The patient also was having intermittent episodes of melena necessitating frequent blood transfusions. The patient was mildly jaundiced, malnourished, and had a marked hepatomegaly. Her initial weight was 106 pounds. The stools were strongly positive for blood and a barium study showed a deformity of the duodenal bulb. Because of an extremely poor appetite and failure to gain weight, the patient was started on a brief (5 to 6 days) intensive course of ACTH despite the evidence of an ulcerating lesion in the duodenum. There was an immediate improvement in appetite, weight gain, euphoria (often seen in patients on steroids), and a general feeling of well-being. Intake increased from 1,500 to 3,500 calories including 210 Gm. of protein daily. The A/G ratio which was initially 3.1 to 2.3 changed to 4.1 to 2.3 (Fig. 1). As the ACTH dosage was reduced the weight receded from the peak of 119 to 112 pounds representing a net gain of 6 pounds. Part of the initial gain in weight represented water retention due to the ACTH but we were convinced that the sharp increase in food intake substantially improved the patient's operability. The improved A/G ratio after celiotomy appears to substantiate the evidence for a gain in lean tissue mass. At operation a large duodenal ulcer which had

eroded into the liver necessitated a gastric resection of the Bancroft type. Re-exploration of the common duct was not attempted. The patient did quite well after operation.

The Chronic Burn Patient.—Patients with open wounds due to burns may present a difficult problem due to anorexia and persistent protein loss from the burned areas. These patients require sufficient protein to make up long-standing deficits as well as to replace daily loss from the open surfaces. Skin grafts often fail to take or may appear to be healing only subsequently to be lost.

Such a problem was presented by a 13-year-old white girl admitted to the hospital 3 months after sustaining full-thickness burns of neck and thorax. The patient was in the hospital for a year during which many grafting procedures were performed. The skin grafts often failed to take or would subsequently break down. Two years after being burned she weighed 95 pounds, was obviously malnourished, yet her serum proteins were 7.3 with an A/G ratio of 4.3 to 3.0. We felt that this was a misleading figure reflecting the tendency to maintain a normal blood protein level in the face of chronic protein depletion. A program of intensive caloric and protein intake was instituted during which the patient received approximately 4,400 calories including 196 Gm. of protein daily (Fig. 2). During this period of 3 weeks the patient was in positive nitrogen balance almost continually and gained 12 pounds. Several subsequent grafting procedures diminished her intake, but 2 months after beginning the high intake the patient had gained a total of 23 pounds and her grafts were well healed. At this time the A/G ratio was 4.5 to 3.1, almost exactly the same as when she was in her original malnourished state.

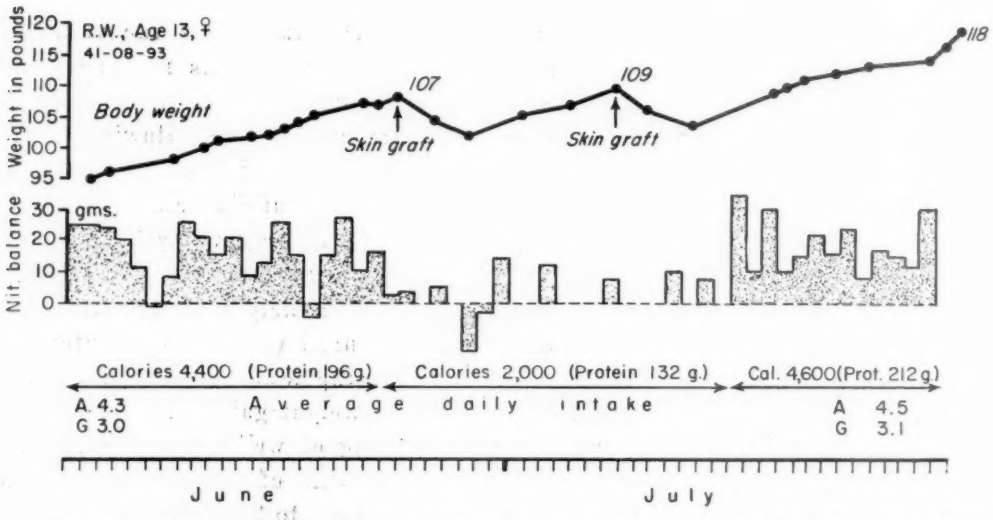
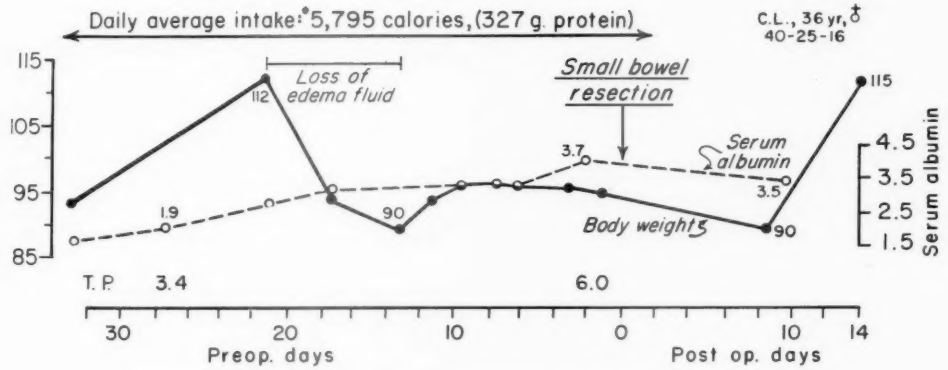


Fig. 2.—Effect of intensive caloric and protein intake on body weight and nitrogen balance of a 13-year-old white girl with old full-thickness burns of neck and thorax. Previous skin grafts had failed or broken down. Net weight gain was 23 pounds and skin grafts have remained healed.

Correction of Severe Malnutrition by Massive Caloric and Protein Intake.—The debilitating effect of a combination of diarrhea, partial small bowel obstruction, and poor intake due to regional ileitis is illustrated by the case of a 36-year-

old white woman admitted one year after a bypass jejunojejunostomy. The patient had intermittent cramping abdominal pain, moderate distention, and severe pitting edema of the legs. She had been on large daily doses of ACTH without benefit. The ACTH was withdrawn gradually and a daily intake of 5,795 calories including 327 Gm. of protein was achieved by the combined use of dietary intake and tube feedings. The patient also was given many transfusions of blood, plasma, and human albumin and received one liter of protein hydrolysate nightly (Fig. 3). Details of the total dietary intake and transfusions are shown. The serum protein of 3.4 Gm. per cent with an albumin of 1.9 on admission reflected the patient's depleted state. After an initial weight gain, the combined effect of ACTH withdrawal and increased plasma proteins resulted in a mobilization of edema fluid and the patient's weight dropped to the original figure although her nutrition was visibly improved. Despite minor flare-ups of abdominal pain and distention she tolerated the heavy intake for one month. The patient was then subjected to celiotomy which revealed multiple areas of fibrosis in the small intestine consistent with a chronic regional ileitis. Six feet of bowel including the old bypass were removed; the patient tolerated the procedure well and convalescence was uneventful. At the time of discharge the patient had gained 30 pounds not including the 12 pounds of edema fluid. Serum proteins were 6.2 and A/G ratio was 4.0 to 2.2.



Daily Caloric and Protein Intake	Calories	Protein
Tube feeding	2,900	175
Oral feeding	2,550	102
Aminosol	345	50
	5,795	327

Total Transfusions	
Blood	3,500 cc.
Plasma	3,250 cc.
Human alb. conc.	250 cc.
Aminosol	33,000 cc.

Fig. 3.—Severe malnutrition and hypoproteinemia corrected with very large daily caloric and protein food intake supplemented with whole blood plasma, human albumin, and protein hydrolysate. Initial weight gain was lost as general edema fluid was mobilized and excreted. Blood proteins increased steadily and final weight gain was 30 pounds.

Weight Gain Due to Intensive Combined Oral and Intravenous Regime.—A most valuable addition to nutritional aids is intravenous fat. The high caloric content (750 calories per 500 c.c.) together with the protein and carbohydrate sparing effect seem effectively to complement intravenous and oral intake. An example (Fig. 4) is that of a 74-year-old white man who entered the hospital because of abdominal pain, difficulty in swallowing, and a 20-pound weight loss during the past 4 months. Twenty-five years ago the patient had

been operated upon for "stomach ulcers" and had done well until the present illness. The patient gave a history of difficulty in swallowing since childhood apparently due to a narrowing of the cervical esophagus. Initial examination showed an anemia and blood in the stools. Barium studies revealed a narrowing of the cervical esophagus without ulceration of the mucosa, and an ulcerated, filling defect of the greater curvature of the stomach just above a gastroenterostomy.

The patient weighed 112 pounds on admission and was put on a thick liquid diet. He ate poorly, however, and was then placed on a regime of 1,000 c.c. of tube feeding, one liter of aminosol, and one bottle of Lipomul in addition to the thick liquid diet. In 3 days the patient gained 4 pounds and after correcting the anemia with whole blood transfusions, a celiotomy was performed. An ulcerating carcinoma of the stomach was found and a high subtotal gastrectomy was performed. The patient's postoperative course was complicated by pneumonia which responded rapidly to penicillin. He subsequently did well.

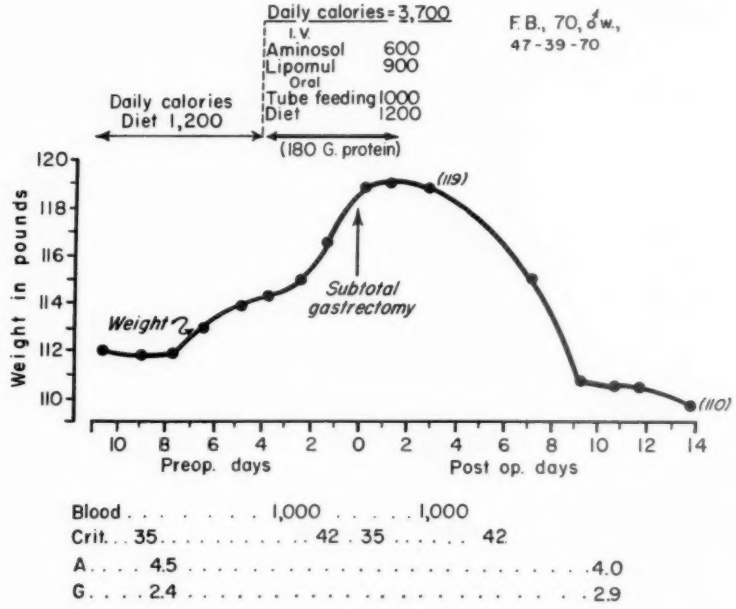


Fig. 4.—Effect of daily protein hydrolysate, intravenous fat, and tube feedings in supplementing limited food intake. This 70-year-old white man had a congenital narrowing of the cervical esophagus which made swallowing difficult. During the 4 months prior to admission he had lost 20 pounds. At operation an ulcerating carcinoma near the greater curvature of the stomach was removed by a high subtotal gastrectomy.

DISCUSSION

It may be gathered that, although the basic problems due to malnutrition are similar, correction of deficits in various patients requires emphasis on different phases of corrective nutritive therapy.

In the first patient use of human albumin provided the best available means for correcting a severe deficit of plasma protein. He also required vigorous whole blood transfusions to bring him into a reasonable condition prior to operation. The initial hematocrit reading of 43 fell to 23 after administration of

human albumin. This tendency to maintain normal hematocrit and blood protein levels in the face of obvious deficits is not at all uncommon and indicates the need for careful evaluation of laboratory values in the light of the known dietary history.

The second patient illustrates the use of ACTH in selected cases. Despite the presence of a large duodenal ulcer, the short period of high corticotrophin therapy caused a feeling of well-being and increased appetite resulting in marked improvement in intake. ACTH is of little value in patients with organic obstruction in the intestinal tract or with painful lesions such as a carcinoma in the oral cavity; however, it may be very helpful in febrile patients or those with anorexia following long periods of malnutrition.

The chronic burn patient illustrates the problem of poor intake combined with protein loss from open wounds. These patients require immense amounts of calories and protein to offset their losses and replenish depleted body reservoirs. Even though they are able to eat, they tire easily of the large quantities of food that are needed. It is here that supplementary tube feedings,[2] often given at night so as not to depress appetite, are of value. It is interesting to note that the A/G ratio upon admission was 4.3 to 3.0. Despite the heavy protein intake and net weight gain of 23 pounds over a 2-month period, the blood protein level remained virtually unchanged (4.5 to 3.1), again showing the need for careful interpretation of these figures.

The severely malnourished patient with regional ileitis (Fig. 3), while similar to the first patient, required almost staggering quantities of protein to correct her deficits. By utilizing every available means of oral and intravenous routes, it was possible to average 327 Gm. of protein daily for one month. The initial A/G ratio of 1.9 to 1.6 rose to 4.0 to 2.2 reflecting the improvement in general nutrition and increase in lean tissue mass.

The final example (Fig. 4) illustrates what can be accomplished in a very short time utilizing intravenous fat in addition to high calory oral feedings and protein hydrolysate by vein. There are good theoretic reasons for believing the fat emulsions are valuable. Fat is high in calories (9 calories per gram), apparently does not irritate the veins, and is not excreted by the kidneys. Experimentally, it has been shown[3] that the amount of dietary fat affects nitrogen metabolism in protein-depleted rats on low calory intake. When the fat content is raised from 10 to 20 per cent of the diet, a significant decrease in nitrogen excretion occurs.

Finally, it must be noted that correction of anemia by blood transfusions is essential. It would appear from Whipple's work[4] that administered nitrogen is first used for regeneration of hemoglobin. If the hematologic deficits are corrected there need be no diversion of protein from replacing other tissue needs.

SUMMARY

Severe malnutrition represents a deficit which if uncorrected, at least in part, prior to operation may jeopardize the patient's condition so that he cannot tolerate the operation planned for him. While the underlying problems are

similar, different patients require emphasis on various aspects of corrective nutritional therapy. Human serum albumin is almost specific in rapidly correcting severe deficits of plasma albumin. ACTH may be very useful in selected patients to give an increased feeling of well-being, improve appetite, or temporarily ameliorate febrile states. The burned patient requires large amounts of calories and protein to offset wound exudates and prevent failure of skin grafts. High protein diets with supplemental tube feedings at night often will be helpful. In severely malnourished patients, it may be necessary to use every available means of alimentation. High calory, high protein diets with supplemental tube feedings in addition to intravenous plasma, protein hydrolysate, fat, and whole blood may be required to achieve a positive nitrogen balance and weight gain.

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Editorial

CONDUCTED BY I. S. RAVDIN, M.D.

Hemorrhoidectomy—Need for a Sound Appraisal

Operative surgery for hemorrhoidal disease has not undergone the repeated critical study which is necessary for the evaluation of any operative procedure. Typically this critical study of other operative procedures has been characterized at the state or national level by the publication of articles and the presentation of papers which report the results of the operation with careful follow-up studies. At the local level, staff conferences and special hospital committees consider the indications employed for any particular operation and the results achieved. Witness, for example, at the national level the great mass of writing concerning the surgical treatment of peptic ulcer, representing a conscientious study of this disease. Even less major operations receive attention as they should: appendectomy, for example. At the local level, it is easy to find a pathologist who will tell you the percentage of normal appendices which may be removed by a staff physician. Hemorrhoidectomy escapes all this.

In current medical literature there are few articles on the subject of hemorrhoidectomy and those that do appear concern only technique. There seem to be no attempts to study the results of the operation or to compare the effectiveness of operative treatment with nonoperative treatment of the disease. In individual hospitals the operation may also escape the attention it deserves. If hospital committees try to evaluate use of the operation they find that the pathologist, generally trusted in these matters, is of no help. Microscopic examination of a bit of mucosa and some dilated veins can have little pertinence to the issue for such a specimen could be removed from almost any middle-aged patient willing to submit to the operation. A conscientious physician cannot find enough information either in the medical literature or in the local hospital to make a sound appraisal of the operation. Thus, a feeling of skepticism is understandable, for this operation is not so well established that it should escape scrutiny.

The crucial question is whether the operation is being done for good reasons. Indications for the operation which are given in modern textbooks appear to be sound but they should obviously not be broadened to include all patients with symptomatic hemorrhoids who come under the care of an occasional surgeon. Any surgeon not manifesting a primary interest in proctology who does a large number of hemorrhoidectomies is a fair target for criticism. Many of his patients who have hemorrhoids could doubtless be treated successfully by conservative methods alone. They may need nothing more than some good advice about

personal hygiene and perhaps a few days of bed rest. A careful soap and water cleansing of the anus after each bowel movement, or at least once a day, is effective in clearing the chronic infection that is generally recognized as the usual cause of painful hemorrhoids. If the hemorrhoids are large, they shrink rapidly when the favorable hemodynamics provided by bed rest are added to a regimen of cleanliness. Is it possible that the painstaking care given to these patients after a hemorrhoidectomy in order to obtain a rapid convalescence would cure most of them even without an operative procedure? A comparison of this course of therapy with the operative treatment would doubtless be enlightening.

F. John Lewis
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Chicago 11, Ill.

ANNOUNCEMENT

Urology Award

The American Urological Association offers an annual award of $1,000 (first prize $500, second prize $300, and third prize $200) for essays on the result of some clinical or laboratory research in Urology. Competition is limited to urologists who have been graduated not more than 10 years and to hospital interns and residents doing research work in Urology.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Chalfonte-Haddon Hall, Atlantic City, New Jersey, April 20-23, 1959.

For full particulars write the Executive Secretary, William P. Didusch, 1120 North Charles Street, Baltimore, Maryland. Essays must be in his hands before Dec. 1, 1958.

Book Review

CONDUCTED BY J. GARROTT ALLEN, M.D.

The Riddle of Stuttering. Charles S. Bluemel. Danville, Ill., 1957, The Interstate Publishing Co. Pp. 142.

Dr. Bluemel is a psychiatrist whose interest in stuttering has extended over a period of many years. He wrote one of the earliest discussions of the problem (1913) which for many years has been used as a text by students of the problem.

His terminology for the various types of stuttering, although not in current usage among many workers in the field, is a reflection of his concern with the problem over many years. Stuttering is divided into two major divisions. The first and earliest manifestion, as found in the child, is stuttering which he defines as nonorganized speech resulting from general immaturity. This is the enthusiastic speech of the child in his third and fourth year who has a greater need for expression than his vocabulary will admit. Such speech is characterized by the gentle and unforced repetition of both sounds of speech and words.

Stammering, on the other hand, is the result of disorganization of poorly organized speech. The disorganization is characteristic of the individual's entire mode of operation. He is diffident, sensitive, selfconscious, indecisive, tense, and easily confused. Primary stammering is the result of a "mutism" of short duration. This is due to the absence of an awareness of the ensuing word in the mind of the speaker. Under such conditions, he will stand and stare. The concept of "mutism" of the mind is the unique contribution of Dr. Bluemel to the thinking upon this problem. The secondary stage of stammering follows fairly closely upon the former. It is characterized by the forcing and facial contortions which are so readily recognized. This is the stage of conscious difficulty on the part of the speaker. He is attempting to break through his "mutism" by muscular force. Without assistance and reduction in intensity, the secondary symptoms take on an element of conditioning. The effort to break through and force out words tends to create additional speech difficulties. This struggle with words and sounds is carried over into the area of silent speech or verbal thinking. The periods of relative fluency of the individual with secondary degree stammering are due to a cessation of environmental stresses.

The genesis of stuttering and stammering is in the early years of life. Dr. Bluemel observes there are very few individuals who begin to stutter after they have reached the seventh year. Both stuttering and stammering have their origins in poorly organized speech. The outward manifestation of the stuttering child is a tendency to interchange sounds of speech, to omit sounds, and to have an inadequate grasp of grammatical construction consonant with his years of maturity. When this child is placed under a condition of stress, stammering results. Factors which influence the organization of speech are parental speech patterns, adequacy of hearing, intelligence of the child, and the presence or absence of brain damage. The poorer the organization of the child's speech, the more susceptible it is to disorganization and stammering under conditions of stress. Stress may be either chronic or acute.

Therapy is a combined approach which places emphasis upon good health, proper diet, psychological assistance, and speech training. Good physical condition increases the individual's ability to withstand stress. Psychological aid enables the subject to adopt a more realistic orientation to his goals and relations to the world of verbal expression. For quick

relief and its associated therapeutic effect, conditions promoting stresses in the patient are controlled and minimized. Speech training has a dual purpose. It seeks to build the patient's confidence through allowing him to experience a degree of success and to counteract the conditioning to which the patient has been subjected over a period of time by hearing his own faulty delivery.

The speech approach is most interesting because it stresses an approach to the sensory modalities rather than the motor. Listening to fluent speech, imitating it inaudibly, and then finally verbal expression before an audience is the prescribed sequence. Its purpose is to effect the reorganization of the disorganized speech.

The surgeon will be interested in this little volume because it can provide him with an index to his patient's sense of well-being. This is not conveyed in the spoken word but rather in the mode of delivery. He will find it helpful in the consideration of patients who do not stutter because of the insight which it gives into the formation of speech and the personality of which speech is but one aspect.

—Duncan R. C. Scott

Calendar of Surgical Meetings

AMERICAN ACADEMY OF NEUROLOGICAL SURGERY. *Annual Meeting,* Nov. 5-8, 1958, Royal York Hotel, Toronto, Ontario, Canada. Secretary, Dr. Robert McLaurin, University of Cincinnati, Cincinnati, Ohio.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA. *Annual Meeting,* Oct. 2-4, 1958, The Drake Hotel, Chicago, Ill. Acting Secretary, Dr. James K. Stack, 700 N. Michigan Ave., Chicago 11, Ill.

AMERICAN CANCER SOCIETY. *Annual Meeting,* Oct. 20-21, 1958, Biltmore Hotel, New York City, N. Y. Secretary, Dr. Scott Hill. Subject, cancer of the colon and rectum.

AMERICAN COLLEGE OF SURGEONS. *Clinical Congress,* Oct. 6-10, 1958, The Conrad Hilton, Chicago, Ill. Secretary, Dr. Michael L. Mason, 40 E. Erie St., Chicago, Ill.

AMERICAN MEDICAL ASSOCIATION. *Annual Meeting,* Dec. 2-5, 1958, Leamington Hotel, Minneapolis, Minn. Deadline for submission of abstracts, Aug. 1, 1958. Secretary, Council on Scientific Assembly, Dr. Thomas G. Hull, 535 North Dearborn St., Chicago 10, Ill.

INTERNATIONAL COLLEGE OF SURGEONS. *Alabama Surgical Division Meeting,* Medical College of Alabama, Birmingham, Oct. 30-31, 1958. Regent of Alabama, Dr. Paul Wolfe Shannon, 1927 First Ave. North, Birmingham 3, Ala. *Mid-Atlantic Regional Meeting,* Homestead Spa, Hot Springs, Va., Nov. 17-18, 1958. Regent of Virginia, Dr. Elbyrne G. Gill, 711 Jefferson St. South, Roanoke 13, Va. *Fifth Annual Congress of the Japanese Section,* Tokyo, Japan, Oct. 17, 1958. For information write to the Secretariat, 1516 Lake Shore Drive, Chicago 10, Ill.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Sept. 26 and 27, 1958, Poland Spring House, Poland Springs, Maine. Deadline for submission of papers, June 20, 1958. Secretary, Dr. J. Gordon Scannell, The Warren Bldg., 275 Charles St., Boston 14, Mass.

SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 12-14, 1959, Denver, Colo. Secretary, Dr. James D. Hardy, University of Mississippi Medical Center, Jackson, Miss.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 9-11, 1958, Boca Raton Hotel and Club, Boca Raton, Fla. Attendance by invitation of membership only. Secretary, Dr. George G. Finney, 2947 St. Paul St., Baltimore 18, Md.

WESTERN SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 20-22, 1958, Hotel Kahler, Rochester, Minn. Deadline for submission of papers, Sept. 1, 1958. Secretary, John T. Reynolds, M.D., 612 N. Michigan Ave., Chicago 11, Ill.